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Art Unit: 1651

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- Structure
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TO: Ralph J Gitomer **Location: 3d65 / 3e71** **Tuesday, March 09, 2004** **Art Unit: 1651** **Phone: 272-0916** **Serial Number: 10 / 029611**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Rem 1A51** **Phone: 272-2504** **jan.delaval@uspto.gov**

Search Notes

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DICTIONARY FILE UPDATES:    7 MAR 2004  HIGHEST RN 659718-58-8

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=> d ide can l27

L27  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   9002-04-4  REGISTRY
CN   Thrombin (8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Blood-coagulation factor II, activated
CN   Blood-coagulation factor IIa
CN   E.C. 3.4.21.5
CN   E.C. 3.4.4.13
CN   Factor IIa
CN   Thrombase
CN   Thrombin JMI
CN   Thrombin-C
CN   Thrombinar
CN   Thrombofort
CN   Thrombostat
CN   Topical
CN   Tropostasin
DR   8050-02-0, 8059-56-1, 9014-41-9, 105881-84-3, 53028-63-0
MF   Unspecified
CI   COM, MAN
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
       CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST,
       CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA,
       MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*,
       TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
           16660 REFERENCES IN FILE CA (1907 TO DATE)
             857 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
           16683 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE   1:  140:164226

REFERENCE   2:  140:161734
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REFERENCE   3:  140:161624

REFERENCE   4:  140:160166

REFERENCE   5:  140:160143

REFERENCE   6:  140:160116

REFERENCE   7:  140:159934

REFERENCE   8:  140:157747

REFERENCE   9:  140:157441

REFERENCE  10:  140:157149


=> d his

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                SET COST OFF

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L1             1 S US20020103107/PN
                 E SOSLAU G/AU
L2            42 S E3-E5
                 E (GP OR GLYCOPROTEIN OR GLYCO PROTEIN)()(IB OR 1B OR (I OR 1)(
L3          2133 S (GP OR GLYCOPROTEIN OR GLYCO PROTEIN)()(IB OR 1B OR (I OR 1)(
                 E GLYCOPROTEIN/CT
                 E E57+ALL
L4           364 S E2
L5           724 S GLYCOPROTEIN#/CW (L) (1B OR IB OR GP1B OR GPIB)
                 E PAR/CT
                 E E6+ALL
L6           280 S E2
L7           308 S E5
L8            50 S E7
L9            92 S E9
L10        13417 S (PAR OR ((PROTEINASE OR PROTEASE)()ACTIVAT?()RECEPTOR)(5A)(1
L11        13414 S (PAR OR ((PROTEINASE OR PROTEASE)()ACTIVAT?()RECEPTOR)()(1 OR
L12        10684 S L10,L11 NOT RECEPTOR
L13         2733 S L10,L11 NOT L12
L14         4881 S L3-L9,L13
                 E DRUG SCREENING/CT
L15        22652 S E3-E5
                 E E3+ALL
L16        28787 S E2,E1+NT
                 E E5+ALL
L17         7824 S E3
                 E E14+ALL
L18         3025 S E1
                 E E2+ALL
                 E DRUG/CT
                 E E10+ALL
L19        15561 S E3
                 E DRUG/CT
L20          882 S E13
L21         8110 S E230+NT OR E231
L22         4500 S E262 OR E263
                 E DRUG SCREENING+ALL/CT
                 E E7+ALL
L23          156 S E2
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L24          78 S L14 AND L15-L23
L25         137 S L14 AND SCREEN?
L26         163 S L24,L25

     FILE 'REGISTRY' ENTERED AT 06:26:53 ON 09 MAR 2004
L27           1 S THROMBIN/CN

     FILE 'HCAPLUS' ENTERED AT 06:27:59 ON 09 MAR 2004
L28       16686 S L27
L29       31055 S THROMBIN
L30         118 S BLOOD()(COAGULAT? OR CLOT?)()FACTOR()(IIA OR II()ACTIVAT?)
L31         463 S THROMBASE OR THROMBINAR OR THROMBOFORT OR THROMBOSTAT OR TROP
L32       31683 S L28-L31
L33          48 S L26 AND L32
L34          33 S L26 AND PLATELET(L)AGGREGAT?
                E CELL AGGREGATION/CT
L35           7 S E3,E4 AND L26
                E E3+ALL
L36          15 S E1+NT AND L26
                E PLATELET/CT
L37          30 S L26 AND E3-E27
                E E28+ALL
L38           7 S L26 AND E3
                E PLATELET/CT
                E E33+ALL
L39          16 S L26 AND E6,E5
                E E4+ALL
L40          27 S L26 AND E5,E4+NT
L41          40 S L26 AND (E12+NT OR E13+NT OR E14+NT)
L42          11 S L26 AND (E16+NT OR E17+NT)
L43          20 S L26 AND (ANTITHROMBO? OR ANTIPLATELET? OR ANTI()(THROMBO? OR
L44          92 S L33-L43
L45           1 S L2 AND L26
L46           1 S L2 AND L44
L47           1 S L1,L45,L46
L48          41 S L2 NOT L47
                SEL DN AN 1 3 10 18
L49           4 S E1-E12 AND L48
L50           5 S L47,L49
L51          91 S L44 NOT L50
L52          32 S L41 AND (PY<=2000 OR PRY<=2000 OR AY<=2000)
                SEL DN AN L52 4 7 19 26 28
L53           5 S E13-E27
L54          10 S L50,L53
L55          59 S L51 NOT L52-L54
                SEL DN AN L55 7 14-18 23 27 29 30 32 33 35 40-43
L56          17 S E28-E70
L57          27 S L54,L56 AND L1-L26,L28-L56
L58          27 S L57 AND (PAR# OR PAR()(1 OR 2 OR 3 OR 4) OR PLATLET?(L)ACTIVA
L59          25 S L58 AND (INHIBIT? OR BLOCK? OR ANTAGON?)
L60          27 S L58,L59

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FILE LAST UPDATED: 8 Mar 2004 (20040308/ED)

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=> d l60 all tot

L60 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2003:736673** HCAPLUS
DN **140:14987**
ED Entered STN: 19 Sep 2003
TI **Proteinase-activated receptors** (**PARs**), **platelets** and angiogenesis
AU Perini, Rafael; Wallace, John L.
CS Mucosal Inflammation Research Group, University of Calgary, Calgary, AB, Can.
SO Drug Development Research (2003), 59(4), 395-399
CODEN: DDREDK; ISSN: 0272-4391
PB Wiley-Liss, Inc.
DT Journal; General Review
LA English
CC 13-0 (Mammalian Biochemistry)
Section cross-reference(s): 1, 2
AB A review. With respect to the role of **proteinase-activated receptors** (**PARs**), few cells have been as thoroughly studied as the **platelet**. **PARs** appear to act as the key **receptors** mediating the pro-**aggregatory** and pro-secretory effects of **thrombin**, but there is considerable variation from species to species in terms of which **PARs** are involved in these processes. In addition to contributing to hemostasis, **platelets** are increasingly being viewed as important contributors to healing and to tumor growth. This can be attributed to the many pro- and anti-angiogenic factors that are stored within **platelets** and are released as sites of injury and new vessel growth. There is emerging evidence for an important role for **PARs** in regulating the release of growth factors from **platelets**, raising the specter that **PARs** may be a rational target for new therapies that will modulate repair processes and tumor growth.
ST review **proteinase activated receptor platelet** angiogenesis
IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PAR** (**proteinase-activated receptors**); **proteinase-activated receptors** and **platelets** and angiogenesis)
IT Angiogenesis
Drug targets
Platelet (blood)
(**proteinase-activated receptors** and **platelets** and angiogenesis)
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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L60 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2003:262709** HCAPLUS
DN **139:127224**
ED Entered STN: 06 Apr 2003
TI **Protease-activated receptor-2 antagonists** and agonists
AU Scarborough, Robert M.
CS Cardiovascular Chemistry, Millennium Pharmaceuticals, Inc., S. San Francisco, CA, 94080, USA
SO Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003), 1(1), 73-82
CODEN: CMCCDP; ISSN: 1568-0169
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review. Interest in the development of specific **antagonists** of the **protease-activated receptors** are significant, however, achieving such goals remain extremely challenging. Considerable efforts have been directed at developing specific **antagonists** of the first elucidated member of this **receptor** family, namely the **thrombin receptor**, **PAR-1**. However, significantly less effort has been directed at the second member of the family, **PAR-2** due in **part** to lack of clarity concerning its **activating protease**(s), and uncertainty concerning its physiol. and pathophysiol. roles in disease pathways. This review will briefly summarize what is known about the **activating protease** (s), the potential (patho)physiol. roles for **PAR-2** and structure-activity relationships that have been developed for **PAR**

-2 agonists and **antagonists** in relationship to agonists and **antagonists** developed for the other **protease-activated receptors.**

ST review **protease activated receptor antagonist** agonist drug target

IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PAR-2** (**proteinase-activated receptor 2**); structure-activity relationships of **protease-activated receptor-2 antagonists** and agonists)

IT **Drug targets**
Human
Structure-activity relationship
(structure-activity relationships of **protease-activated receptor-2 antagonists** and agonists)

RE.CNT 93 THERE ARE 93 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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L60 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2003:262707** HCAPLUS
DN **139:127222**
ED Entered STN: 06 Apr 2003
TI Non-peptidic small-molecule **antagonists** of the human **platelet thrombin receptor PAR-1**
AU Selnick, H. G.; Barrow, J. C.; Nantermet, P. G.; Connolly, T. M.
CS Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SO Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003), 1(1), 47-59

CODEN: CMCCDP; ISSN: 1568-0169
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review. The **thrombin receptor** on human **platelets** is the first member identified of a new family of G-protein coupled **receptors** referred to as **protease activated receptors (PARs)**. These **receptors** are **activated** by a unique mechanism involving proteolytic cleavage of a portion of the extracellular domain to generate a new N-terminus which then acts as a **tethered** or intramol. ligand (agonist) for the **receptor.** The hexapeptide SFLLRN-NH2 comprising the new N-terminus is referred to as the **Thrombin Receptor Activating** Peptide, or "TRAP" **Thrombin** is the most potent agonist for **platelet aggregation** and selective **blockade** of the intramol. **activation** step without effecting the proteolytic activity of **thrombin** should result in moderation of **platelet activation** and **aggregation** without interfering with the other coagulation cascade effects of **thrombin. Screening** of combinatorial libraries identified a novel, non-peptide **PAR-1 thrombin receptor antagonist.** Examination of structure-activity relationships revealed that portions of the mol. could be replaced resulting in simpler mols. of lower mol. weight that were at the same time more potent. Mols. in this series were effective **antagonists** of TRAP-stimulated **platelet activation**, but had limited activity when **thrombin** was the agonist. Addnl. directed **screening** and subsequent lead refinement resulted in a second series of isoxazole based compds. Some of the resultant mols. were potent **PAR-1 antagonists** that were effective against both TRAP- and **thrombin**-stimulated **receptor activation.** These compds. do not **inhibit** the proteolytic effects of **thrombin** but rather interfere with the intramol. binding of the **tethered** ligand (SFLLRN) to the transmembrane portion of the **thrombin receptor.** They represent promising leads for future explorations of **antithrombotic** activity of **thrombin receptor antagonists.**
ST review nonpeptide mol **antagonist antiplatelet thrombin receptor PAR1**

IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PAR-1 (proteinase-activated receptor 1**); non-peptidic small-mol. **antagonists** of human **platelet thrombin receptor PAR-1**)

IT **Anticoagulants**
Combinatorial library
Drug screening
Human
Platelet aggregation inhibitors
Structure-activity relationship
(non-peptidic small-mol. **antagonists** of human **platelet thrombin receptor PAR-1**)

IT **9002-04-4, Thrombin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(non-peptidic small-mol. **antagonists** of human **platelet thrombin receptor PAR-1**)

RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L60 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2003:262705** HCAPLUS
DN **139:127220**
ED Entered STN: 06 Apr 2003
TI Discovery of potent peptide-mimetic **antagonists** for the human **thrombin receptor, protease-activated receptor-1 (PAR-1)**
AU Maryanoff, Bruce E.; Zhang, Han-Cheng; Andrade-Gordon, Patricia; Derian, Claudia K.
CS Drug Discovery, Johnson and Johnson Pharmaceutical Research and Development, Spring House, PA, 19477-0776, USA
SO Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003), 1(1), 13-36
CODEN: CMCCDP; ISSN: 1568-0169

PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 27, 28, 34
AB A review. **Protease-activated receptors** (**PARs**) represent a unique family of seven-transmembrane G-protein-coupled **receptors**, which are enzymically cleaved to expose a new extracellular N-terminus that acts as a **tethered activating** ligand. **PAR-1** is cleaved and **activated** by the serine **protease** α-**thrombin**, is expressed in various tissues (e.g., **platelets** and vascular cells), and is involved in cellular responses associated with hemostasis, proliferation, and tissue injury. By using a de novo design approach, we have discovered a series of potent heterocycle-based peptide-mimetic **antagonists** of **PAR-1**, exemplified by advanced leads RWJ-56110 and RWJ-58259. These compds. are potent, selective **PAR-1 antagonists**, devoid of **PAR-1** agonist and **thrombin inhibitory** activity: they bind to **PAR-1**, interfere with calcium mobilization and cellular functions associated with **PAR-1**, and do not affect **PAR-2**, **PAR-3**, or **PAR-4**. RWJ-56110 was determined to be a direct **inhibitor** of **PAR-1 activation** and internalization, without affecting **PAR-1** N-terminal cleavage. At high concns. of α-**thrombin**, RWJ-56110 fully **blocked activation** responses in human vascular cells, but not in human **platelets**; whereas, at high concns. of TRAP-6, RWJ-56110 **blocked activation** responses in both cell types. This result is consistent with the presence of another **thrombin receptor** on human **platelets**, namely **PAR-4**. RWJ-56110 and RWJ-58259 clearly interrupt the binding of a **tethered** ligand to its **receptor**. RWJ-58259 demonstrated antirestenotic activity in a rat balloon angioplasty model and **antithrombotic** activity in a cynomolgus monkey arterial injury model. Such **PAR-1 antagonists** should not only serve as useful tools to delineate the physiol. and pathophysiol. roles of **PAR-1**, but also may have therapeutic potential for treating thrombosis and restenosis in humans.
ST review peptidomimetic **thrombin receptor antagonist protease PAR1 antithrombotic** restenosis
IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PAR-1** (**proteinase-activated receptor 1**); discovery of potent peptide-mimetic **antagonists** for human **thrombin receptor**, **protease-activated receptor-1** (**PAR-1**))
IT Artery
(angioplasty; discovery of potent peptide-mimetic **antagonists** for human **thrombin receptor**, **protease-activated receptor-1** (**PAR-1**))
IT Peptidomimetics
(**antagonists**; discovery of potent peptide-mimetic **antagonists** for human **thrombin receptor**, **protease-activated receptor-1** (**PAR-1**))
IT **Anticoagulants**
Drug design
Human

Thrombosis
(discovery of potent peptide-mimetic **antagonists** for human **thrombin receptor, protease-activated receptor-1 (PAR-1)**)

IT Artery, disease
(restenosis; discovery of potent peptide-mimetic **antagonists** for human **thrombin receptor, protease-activated receptor-1 (PAR-1)**)

IT 252889-88-6, RWJ-56110 315203-31-7, RWJ-58259
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(discovery of potent peptide-mimetic **antagonists** for human **thrombin receptor, protease-activated receptor-1 (PAR-1)**)

RE.CNT 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L60 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2003:262704** HCAPLUS
DN **139:127219**
ED Entered STN: 06 Apr 2003
TI Peptide-derived **protease-activated receptor-1** (**PAR-1**) **antagonists**
AU Seiler, Steven M.; Bernatowicz, Michael S.
CS Department of Vascular Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08534, USA
SO Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003), 1(1), 1-11
CODEN: CMCCDP; ISSN: 1568-0169
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 34
AB A review. **Protease activated receptor-1** (**PAR-1**) is a G-coupled **receptor** cleaved by **thrombin** and other **proteases** to expose a new N-terminus, a "**tethered** ligand", that **activates** the **receptor.** Independently of proteolytic cleavage, peptides similar to the new N-terminus also **activate** the **receptor**, and structure activity relationships for the **activating** peptides have been extensively studied. Modification of **activating** peptides led to rationally designed peptide **antagonists.** The more potent peptide **antagonists** were

N-terminal and 3-position modifications of the agonist peptides. The resulting **PAR-1 antagonists** have proved useful in pharmacol. studies resolving the contribution of **PAR-1** signaling mechanisms relative to other **PARs** in **platelets**, vascular endothelial and other cell types. High affinity peptide agonists and **antagonists** have been radiolabeled and proven useful in binding assays. **Screening** of combinatorial libraries and compound collections using the radioligands have identified non-peptide **antagonists** of several different chemotypes. When the "**thrombin receptor**" (**PAR-1**) was first cloned and its mechanism of **activation** elucidated, there was great enthusiasm for the **receptor** as a drug target. The use of peptide agonists and **antagonists** has made possible much progress in our understanding of the role of this **receptor.**

ST review peptide **protease receptor PAR1** **antagonist** structure activity thrombosis

IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PAR-1** (**proteinase-activated receptor 1**); structure-activity relationship of peptide-derived **protease-activated receptor -1** (**PAR-1**) **antagonists**)

IT **Thrombosis**
(arterial; structure-activity relationship of peptide-derived **protease-activated receptor-1** (**PAR-1**) **antagonists**)

IT Artery, disease
(restenosis; structure-activity relationship of peptide-derived **protease-activated receptor-1** (**PAR-1**) **antagonists**)

IT Combinatorial library
Drug screening
Human
Peptide library
Signal transduction, biological
Structure-activity relationship
(structure-activity relationship of peptide-derived **protease-activated receptor-1** (**PAR-1**) **antagonists**)

IT 322765-75-3, BMS-200261
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-activity relationship of peptide-derived **protease-activated receptor-1** (**PAR-1**) **antagonists**)

RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L60 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2003:184200** HCAPLUS
ED Entered STN: 11 Mar 2003
TI Discovery and optimization of potent orally active small molecular **thrombin receptor PAR-1 antagonists**
AU Kawahara, Tetsuya; Suzuki, Syuichi; Kogushi, Motoji; Matsuoka, Tosiyuki; Kobayashi, Hiroko; Kajiwara, Akiharu; Hishinuma, Ieharu
CS Drug research laboratory, Eisai Co.,Ltd, Tukuba, 300-2635, Japan

SO Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-234 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69DSA4
DT Conference; Meeting Abstract
LA English
AB **Thrombin**, a trypsin-like serine **protease**, is centrally involved in hemostasis, and also promotes diverse cellular responses such as **platelet aggregation**, lymphocyte mitosis, monocyte chemotaxis, and vascular smooth muscle proliferation. These actions are mediated by proteolytically-**activated thrombin receptors** (**protease-activated receptors**: **PARs**). A non-peptide small mol. **PAR-1 antagonist** (ER-97719-15) was obtained from high throughput **screening** using a **receptor** binding assay system. Through optimization of ER-97719-15, we found three types of compound with moderate **PAR-1 antagonistic** activity. In particular the indolin derivative ER-121958-06 **inhibited** human PRP **aggregation** by **thrombin** at 21nM. Furthermore ER-121958-06(10 mg/kg p.o.) **inhibited** ex vivo **aggregation** induced by **thrombin** in the guinea pig. The SAR and biol. evaluation of this series of compds. are described.

L60 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2002:696020** HCAPLUS
DN **137:227727**
ED Entered STN: 13 Sep 2002
TI Protein, gene and cDNA sequences of a novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide
IN Darrow, Andrew; Derian, Claudia; Addo, Michael; Andrade-Gordon, Patricia
PA Ortho-McNeil Pharmaceutical, Inc., USA
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K014-705
ICS C12N015-12; C07K016-28; G01N033-50; C12N005-10
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 6, 13
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002070564	A2	20020912	WO 2002-US5946	20020226
	WO 2002070564	A3	20030227		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1363947	A2	20031126	EP 2002-713702	20020226
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2001-798279	A	20010302		
	WO 2002-US5946	W	20020226		

AB This invention provides protein, gene and cDNA sequences of a novel guinea pig **PAR-4** and its **activating** peptide. The guinea pig DNA and protein are useful for the development of models of human **platelet aggregation.** The invention further

relates to an animal model to assess the role of **PAR antagonists** in thrombosis.

ST gene cDNA sequence Cavia **proteinase activated receptor PAR4**

IT **Receptors**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(**PAR-4** (**proteinase-activated receptor 4**); protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)

IT **Platelet (blood)**
(**aggregation**, **PAR-4** inducing; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)

IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(encoding **PAR-4**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)

IT Genetic vectors
(for expressing **PAR-4**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)

IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(monoclonal, to **PAR-4**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)

IT **Drug screening**
Guinea pig (Cavia porcellus)
Human
Molecular cloning
Protein sequences
cDNA sequences
(protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)

IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(to **PAR-4**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)

IT 459226-13-2P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(amino acid sequence; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)

IT 459226-10-9
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating**

peptide)
IT 58-64-0, ADP, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(degranulation; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)
IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mobilization; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)
IT 459226-11-0P 459226-12-1P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(nucleotide sequence; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)
IT 212277-69-5, GenBank AF080215 385282-18-8, GenBank AF055917
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(protein, gene and cDNA sequences of a novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)
IT 459232-25-8 459232-26-9
RL: PRP (Properties)
(unclaimed nucleotide sequence; protein, gene and cDNA sequences of a novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)
IT 459232-27-0 459232-28-1 459232-29-2
RL: PRP (Properties)
(unclaimed protein sequence; protein, gene and cDNA sequences of a novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)
IT 141136-83-6 213018-42-9 225779-44-2 459123-98-9 459123-99-0
RL: PRP (Properties)
(unclaimed sequence; protein, gene and cDNA sequences of a novel guinea pig **proteinase-activated receptor 4** (**PAR-4**) and its **activating** peptide)

L60 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2002:675811** HCAPLUS
DN **137:195614**
ED Entered STN: 08 Sep 2002
TI Compositions and methods for preventing **platelet aggregation** comprising histones
IN Class, Reiner; **Soslau, Gerald**; Zeppezauer, Michael
PA Philadelphia, Health and Education Corporation, USA; Symbiotec G.m.b.H.
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-70
ICS A61K009-22; A61K031-00; A61K051-08; A61K009-50; A61F002-00; B01J013-08; C12N011-02
CC 1-12 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002067907	A1	20020906	WO 2002-US5157	20020222

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1370248 A1 20031217 EP 2002-706353 20020222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI US 2001-270759P P 20010222
WO 2002-US5157 W 20020222

AB Compns. and methods for preventing **platelet aggregation** and treating cardiovascular disease via histone compds. are provided. An assay for **platelet aggregation** using angonist and **antagonist** is described.

ST **platelet aggregation inhibitor** histone

IT Histones
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(H1; compns. and methods for preventing **platelet aggregation**)

IT Histones
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(H2A; compns. and methods for preventing **platelet aggregation**)

IT Histones
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(H2B; compns. and methods for preventing **platelet aggregation**)

IT Histones
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(H3; compns. and methods for preventing **platelet aggregation**)

IT Histones
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(H4; compns. and methods for preventing **platelet aggregation**)

IT **Platelet aggregation inhibitors**
(compns. and methods for preventing **platelet aggregation**)

IT Histones
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. and methods for preventing **platelet aggregation**)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Hale; US 5607691 A 1997 HCAPLUS
(2) Ito; US 5126140 A 1992 HCAPLUS
(3) Yen; US 5616311 A 1997 HCAPLUS

L60 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:575738 HCAPLUS
DN 137:103859
ED Entered STN: 02 Aug 2002

TI **Screening** assay for **anti-thrombotic/ anti-platelet** activity
IN **Soslau, Gerald**
PA USA
SO U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM C12Q001-56
ICS A61K031-00
NCL 514001000
CC 1-1 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002103107	A1	20020801	US 2001-29611	20011221 <--
PRAI US 2000-257067P	P	20001221		

AB A method for **screening** for **anti-thrombotic/ anti-platelet** agents is provided where the method is based on **inhibition** of the **GP Ib, PAR-1** and/or **PAR-4** pathways by the potential **antithrombotic/anti-platelet** agent.
ST **screening** assay thrombotic **platelet** activity
IT **Glycoproteins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**GPIb**; **screening** assay for **anti-thrombotic/anti-platelet** activity)
IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PAR-1** (**proteinase-activated receptor 1**); **screening** assay for **anti-thrombotic/anti-platelet** activity)
IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PAR-4** (**proteinase-activated receptor 4**); **screening** assay for **anti-thrombotic/anti-platelet** activity)
IT **Platelet (blood)**
(**aggregation**; **screening** assay for **anti-thrombotic/anti-platelet** activity)
IT Biological transport
(efflux; **screening** assay for **anti-thrombotic/anti-platelet** activity)
IT **Cell aggregation**
(**platelet**; **screening** assay for **anti-thrombotic/anti-platelet** activity)
IT **Anticoagulants**
Drug screening
Platelet (blood)
Platelet aggregation inhibitors
(**screening** assay for **anti-thrombotic/anti-platelet** activity)
IT 56-65-5, 5'-ATP, biological studies 7440-70-2, Calcium, biological studies **9002-04-4, Thrombin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**screening** assay for **anti-thrombotic/anti-platelet** activity)

L60 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2002:171599** HCAPLUS

DN **136:226788**
ED Entered STN: 08 Mar 2002
TI Therapeutics and diagnostics based on a novel signal transduction system in **platelets**
IN Ramakrishnan, Vanitha; Phillips, David
PA Cor Therapeutics, Inc., USA
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A01K067-027
ICS G01N033-86; A61P007-00
CC 1-8 (Pharmacology)
Section cross-reference(s): 9, 15
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002017711	A2	20020307	WO 2001-US26936	20010831 <--
	WO 2002017711	A3	20030227		
	WO 2002017711	C2	20031030		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2001086900	A5	20020313	AU 2001-86900	20010831 <--
PRAI	US 2000-229047P	P	20000831 <--		
	US 2000-230566P	P	20000831 <--		
	WO 2001-US26936	W	20010831		

AB The present invention relates to therapeutics and diagnostics that take advantage of a novel signal transduction pathway in **platelets.** In addition, the present invention provides methods for identifying agents that modulate activities mediated by the novel transduction pathway including **platelet activation** and thrombosis.
ST signal transduction blood **platelet** sequence **glycoprotein GPV** diagnostic **antithrombotic**
IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study) (CD42a; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT Cytometry
(FACS (fluorescence-**activated** cell sorting); antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT **Glycoproteins**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (**GP** IX; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT **Platelet (blood)**
(**GP** V-null; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT **Glycoproteins**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(**GP** Vfl; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT **Glycoproteins**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (**GPIb**; antithromotics and diagnostics based on a novel signal

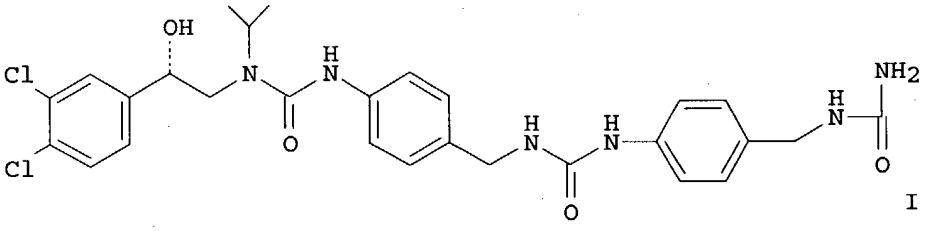
transduction system in **platelets**)
IT **Glycoproteins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(V; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT **Platelet (blood)**
(**activation**; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT Diagnosis
(agents; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT Transgene
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(animal expressing; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT **Anticoagulants**
Blood analysis
Blood coagulation
Diagnosis
Drug delivery systems
Drug screening
Genetic vectors
Molecular cloning
Mouse
Platelet aggregation inhibitors
Protein sequences
Rabbit
Signal transduction, biological
cDNA sequences
(antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT **Thrombin receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT Antibodies
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT Mutation
(deletion, knockout; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT Immunoassay
(immunoblotting; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT Animal
(transgenic **GP** V knockout; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT 71142-71-7, Ppack
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(-inactivated **thrombin**; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT **9002-04-4, Thrombin**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT **9002-04-4D, Thrombin**, analogs
RL: PAC (Pharmacological activity); BIOL (Biological study)
(antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
IT 402907-62-4

RL: PRP (Properties)
(unclaimed nucleotide sequence; therapeutics and diagnostics based on a novel signal transduction system in **platelets**)

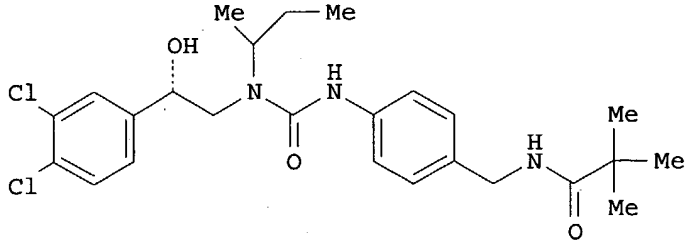
IT 402907-63-5
RL: PRP (Properties)
(unclaimed protein sequence; therapeutics and diagnostics based on a novel signal transduction system in **platelets**)

IT 259085-34-2 259085-35-3 259085-36-4 259085-37-5 259085-38-6
402907-57-7 402907-58-8 402907-59-9 402907-60-2 402907-61-3
402907-64-6 402907-65-7
RL: PRP (Properties)
(unclaimed sequence; therapeutics and diagnostics based on a novel signal transduction system in **platelets**)

L60 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2001:746574** HCAPLUS
DN **136:112200**
ED Entered STN: 12 Oct 2001
TI Discovery and initial structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**
AU Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Ngo, P. L.; Young, M. B.; Pellicore, J. M.; Breslin, M. J.; Hutchinson, J. H.; Freidinger, R. M.; Condra, C.; Karczewski, J.; Bednar, R. A.; Gaul, S. L.; Stern, A.; Gould, R.; Connolly, T. M.
CS Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SO Bioorganic & Medicinal Chemistry Letters (2001), 11(20), 2691-2696
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 25, 27, 28, 34
GI



I



II

AB **Thrombin** is the most potent agonist of **platelet activation**, and its effects are predominantly mediated by **platelet thrombin receptors.** Therefore, **antagonists** of the **thrombin receptor** have potential utility for the treatment of thrombotic disorders. **Screening** of combinatorial libraries revealed (I) to be a potent **antagonist** of the **thrombin receptor.** Modifications of this structure produced (II), which **inhibits thrombin receptor** stimulated secretion and **aggregation** of **platelets.**

ST **antiplatelet** trisubstituted ureas **PAR1 receptor antagonist** structure; **thrombin receptor antagonist** structure trisubstituted ureas

IT **Receptors**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(**PAR-1** (**proteinase-activated receptor 1**), **antagonists**; discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)

IT Structure-activity relationship
(**PAR-1 receptor-antagonizing**; discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)

IT **Thrombin receptors**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(**antagonists**; discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)

IT Combinatorial library
Drug design
Drug screening
Platelet aggregation inhibitors
(discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)

IT Structure-activity relationship
(**platelet aggregation-inhibiting**; discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)

IT Structure-activity relationship
(**thrombin-inhibiting, thrombin receptor**; discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)

IT 390405-90-0
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)

IT 57-13-6DP, Urea, trisubstituted 147-85-3DP, L-Proline, -derived ureas 374929-06-3P 374929-08-5P 390404-92-9P 390405-02-4P 390405-06-8P 390405-16-0P 390405-34-2P 390406-33-4P 390406-68-5P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**)

antagonists)
IT 6287-38-3 6859-99-0, 3-Piperidinol 40499-83-0, 3-Pyrrolidinol
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)
IT 52909-94-1P 173086-67-4P 390406-20-9P 390406-53-8P
RL: PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)
IT 374929-07-4P 374929-09-6P 374929-10-9P 374929-11-0P 374929-12-1P
374929-13-2P 374929-18-7P 390405-00-2P 390405-04-6P 390405-08-0P
390405-10-4P 390405-12-6P 390405-14-8P 390405-24-0P 390405-67-1P
390406-05-0P 390406-06-1P 390406-09-4P 390406-13-0P 390406-23-2P
390406-29-8P 390406-31-2P 390406-51-6P 390406-55-0P 390406-57-2P
390406-65-2P 390406-73-2P 390406-77-6P 390406-82-3P 390406-87-8P
390406-90-3P 390406-92-5P 390407-23-5P 390407-30-4P 390407-32-6P
390407-36-0P 390407-42-8P 390407-55-3P 390407-95-1P 390407-99-5P
390408-01-2P 390408-08-9P 390408-09-0P 390408-12-5P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)
IT 104-63-2, N-Benzylethanolamine 105-07-7 147-85-3, L-Proline, reactions
874-42-0 2181-42-2, Trimethylsulfonium iodide 2632-10-2 5973-71-7
6334-18-5 10203-08-4 20555-91-3, 3,4-Dichloro-iodobenzene 20879-18-9
24964-64-5 34036-07-2 71026-66-9 74003-55-7 94838-55-8
94838-59-2 374929-25-6 374929-32-5 390406-08-3 390406-26-5
390406-91-4 390406-94-7 390406-97-0 390406-99-2 390407-01-9
390407-03-1 390407-06-4 390407-09-7 390407-11-1 390407-13-3
390407-15-5 390408-19-2 390408-20-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)
IT 1855-36-3P 13692-15-4P 13906-62-2P 52695-39-3P 78982-97-5P
111991-13-0P 115186-37-3P 158397-38-7P 390404-98-5P 390405-95-5P
390405-98-8P 390406-02-7P 390406-28-7P 390406-30-1P 390406-40-3P
390406-43-6P 390406-45-8P 390406-61-8P 390406-71-0P 390406-80-1P
390407-76-8P 390407-80-4P 390407-82-6P 390407-84-8P 390407-86-0P
390407-88-2P 390407-90-6P 390407-92-8P 390408-04-5P 390408-06-7P
390408-07-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)
IT 185028-91-5 185028-98-2
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(lead structure of **PAR-1 antagonists**; discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)
IT 141923-41-3
RL: PAC (Pharmacological activity); BIOL (Biological study)
(mimics; discovery and structure-activity relationships of trisubstituted ureas as **thrombin receptor** (**PAR-1**) **antagonists**)
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Ahn, H; Bioorg Med Chem Lett 1999, V9, P2073 HCAPLUS
(2) Alexopoulos, K; Amino Acids 1998, V15, P211 HCAPLUS
(3) Andrade-Gordon, P; Proc Natl Acad Sci 1999, V96, P12257 HCAPLUS
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(8) Brown, H; Acc Chem Res 1992, V25, P16 HCAPLUS
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L60 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2001:661483** HCAPLUS
DN **135:216013**
ED Entered STN: 10 Sep 2001
TI **GPIb**-lipid bond construct and use thereof
IN Ikeda, Yasuo; Saito, Hiroshi; Mukai, Hiromichi; Mori, Yoshiyuki; Murata, Mitsuru
PA Welfide Corporation, Japan
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM C07K014-475
ICS A61K038-14; A61K047-34; A61K009-127; A61K047-24; A61K047-26; A61K047-14; A61K047-28; A61K045-00; A61K049-06; A61K049-04; A61K049-14; A61K051-08; A61P007-02; A61P007-04; A61P009-00; A61P029-00; A61K101-02; A61K123-00
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001064743	A1	20010907	WO 2001-JP1635	20010302 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 2001036062 A5 20010912 AU 2001-36062 20010302 <--
EP 1262490 A1 20021204 EP 2001-908262 20010302 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
US 2003113262 A1 20030619 US 2002-220610 20021021 <--
PRAI JP 2000-57449 A 20000302 <--
WO 2001-JP1635 W 20010302

AB Disclosed are a construct wherein a **glycoprotein (GP) Ib** is bonded to a lipid via a polyalkylene oxide; and a complex (**GPIb** lipid complex) containing this bond construct and a free lipid. This **GPIb** lipid complex is expected as widely applicable in practice as, for example, a substitute for **platelets**, drugs (preventives and remedies for vascular lesion, vascular damage, thrombosis, etc.), diagnostics for vWF deficiency, etc., biol. and medicinal reagents, and reagents for **screening platelet aggregation inhibitors** and **antithrombotic** agents. Moreover, the **GPIb** lipid complex is highly useful as diagnostics or remedies for examining vascular damage or thrombogenetic sites. Furthermore, the **GPIb** lipid complex is excellent in the retention properties in the blood and can exert sustained pharmacol. effects. The above-described bond construct is highly valuable as the active ingredient of the **GPIb** lipid complex.

ST glycolipoprotein lipid complex liposome blood disorder

IT Glycolipoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**GPIb**, complexes; liposomes containing **GPIb** -polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT **Platelet (blood)**
(artificial; liposomes containing **GPIb**-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(complexes with **GPIb** and lipids; liposomes containing **GPIb**-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(complexes, with **GPIb** and lipids; liposomes containing **GPIb**-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT Fatty acids, biological studies
Glycerides, biological studies
Glycophospholipids
Phospholipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(complexes, with **GPIb**; liposomes containing **GPIb** -polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT Anti-inflammatory agents
Anticoagulants
Blood vessel, disease
Platelet aggregation inhibitors
Vasoconstrictors
Vasodilators
Von Willebrand's disease
(liposomes containing **GPIb**-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT Drug delivery systems

(liposomes; liposomes containing **GPIb**-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT **109319-16-6**, Von Willebrand's factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(liposomes containing **GPIb**-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT 57-88-5D, Cholesterol, complexes with **GPIb** and PEG 9003-11-6D, Ethylene oxide-propylene oxide copolymer, complexes with **GPIb** and lipids 25322-68-3D, Polyethylene glycol, complexes with **GPIb** and lipids 25322-69-4D, Polypropylene glycol, complexes with **GPIb** and lipids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liposomes containing **GPIb**-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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L60 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2001:617855** HCAPLUS
DN **135:175384**
ED Entered STN: 24 Aug 2001
TI Methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G
IN Sambrano, Gilberto; Coughlin, Shaun R.
PA The Regents of the University of California, USA
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-55
ICS A61K039-395; G01N033-50; C12N015-09; A61K038-06; A61P009-10; A61P029-00; A61P009-00
CC 1-8 (Pharmacology)
Section cross-reference(s): 15

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001060401	A1	20010823	WO 2001-US4987	20010214

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-506431 A2 20000217
AB The present invention provides methods for modulating cathepsin G-mediated **PAR4 activation** and/or **platelet**

activation. Further, the invention provides methods for **screening** agents which may modulate cathepsin G-mediate **PAR4 activation** and/or **platelet activation.**

ST **protease activated receptor 4** cathepsin G modulator; **PAR4 activation** cathepsin G modulator **platelet**; **platelet activation** **PAR4** cathepsin G modulator

IT **Receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**PAR-4** (**proteinase-activated receptor 4**); methods of modulating **protease -activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT **Platelet (blood)**
(**activation**; methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT **Platelet (blood)**
(**aggregation**, in cathepsin G-mediated **PAR4 activation** determination; methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Heart, disease
(angina pectoris, unstable, treatment; methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Biological transport
(calcium, in cathepsin G-mediated **PAR4 activation** determination; methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Lung, disease
(embolism, treatment; methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Organ, animal
(failure, treatment; methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Phosphoinositides
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hydrolysis, in cathepsin G-mediated **PAR4 activation** determination; methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Heart, disease
(infarction, treatment; methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Anti-inflammatory agents
Anticoagulants

Drug delivery systems
Drug screening
Neutrophil
Platelet aggregation inhibitors
(methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT **Cell aggregation**
(**platelet**, in cathepsin G-mediated **PAR4 activation** determination; methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Cell **activation**
(**platelet**; methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Brain, disease
(stroke, treatment; methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to **PAR4**, cathepsin G-mediated **PAR4 activation inhibition** by; methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT **Thrombosis**
Transplant and Transplantation
(treatment; methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT 59880-97-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cathepsin G release from neutrophils stimulation by; methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(in cathepsin G-mediated **PAR4 activation** determination; methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)

IT 56645-49-9, Cathepsin G
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G and **platelet activation** in relation to

effect of neutrophils)
IT 56-65-5, 5'-ATP, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(secretion by **platelets** of, in cathepsin G-mediated **PAR4 activation** determination; methods of modulating **protease-activated receptor-4** (**PAR4**) **activation** via cathepsin G and **platelet activation** in relation to effect of neutrophils)
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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(2) Kahn; JOURNAL OF CLINICAL INVESTIGATION 1999, V103(6), P879 HCAPLUS
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L60 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2001:612021** HCAPLUS
DN **136:548**
ED Entered STN: 23 Aug 2001
TI **Thrombin receptor (PAR-1) antagonists.** Solid-phase synthesis of indole-based peptide mimetics by anchoring to a secondary amide
AU Zhang, H.-C.; McComsey, D. F.; White, K. B.; Addo, M. F.; Andrade-Gordon, P.; Derian, C. K.; Oksenberg, D.; Maryanoff, B. E.
CS Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477-0776, USA
SO Bioorganic & Medicinal Chemistry Letters (2001), 11(16), 2105-2109
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-12 (Pharmacology)
Section cross-reference(s): 34
AB A novel, 10-step, solid-phase method, based on a secondary amide linker, was developed to construct a diverse library of indole-based SFLLR peptide mimetics as **thrombin receptor (protease-activated receptor 1, PAR-1) antagonists.** The key steps include stepwise reductive alkylation, urea formation, and Mannich reaction. **Screening** of the library led to a quick development of the SAR and the significant improvement of **PAR-1** activity.
ST peptidomimetic prepn **thrombin receptor antagonist**
IT **Receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**PAR-1 (proteinase-activated receptor 1**); solid-phase synthesis of indole-based peptidomimetic **thrombin receptor (PAR-1) antagonists** by anchoring to a secondary amide and structure activity studies)
IT Alkylation
(reductive; solid-phase synthesis of indole-based peptidomimetic **thrombin receptor (PAR-1) antagonists** by anchoring to a secondary amide and structure activity studies)
IT Mannich reaction
Peptide library

Peptidomimetics
Structure-activity relationship
(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor** (**PAR-1**) **antagonists** by anchoring to a secondary amide and structure activity studies)

IT **Thrombin receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor** (**PAR-1**) **antagonists** by anchoring to a secondary amide and structure activity studies)

IT 252889-86-4, RWJ-53052
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor** (**PAR-1**) **antagonists** by anchoring to a secondary amide and structure activity studies)

IT 252889-87-5P 252889-88-6P 316149-51-6P 316149-59-4P 316149-65-2P
316149-71-0P 316150-31-9P 316150-40-0P 316150-46-6P 316150-75-1P
316151-44-7P 316151-47-0P 316151-49-2P 375392-69-1P 375392-70-4P
375392-71-5P 375392-72-6P 375392-73-7P 375392-74-8P 375392-75-9P
375392-76-0P 375392-77-1P 375392-78-2P 375392-79-3P 375392-80-6P
375392-81-7P 375392-82-8P 375392-83-9P
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor** (**PAR-1**) **antagonists** by anchoring to a secondary amide and structure activity studies)

IT 57-13-6, Urea, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor** (**PAR-1**) **antagonists** by anchoring to a secondary amide and structure activity studies)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L60 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2001:455649** HCAPLUS
DN **135:164961**
ED Entered STN: 24 Jun 2001
TI Unique pathway of **thrombin**-induced **platelet aggregation** mediated by **glycoprotein Ib**
AU **Soslau, Gerald**; Class, Reiner; Morgan, Doris A.; Foster, Carolyn; Lord, Susan T.; Marchese, Patrizia; Ruggeri, Zaverio M.
CS Departments of Biochemistry, Medicine, Division of Hematology/Oncology, MCP Hahnemann School of Medicine, Philadelphia, PA, 19102, USA
SO Journal of Biological Chemistry (2001), 276(24), 21173-21183
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 13-5 (Mammalian Biochemistry)
AB **Thrombin** plays a central role in normal and abnormal hemostatic processes. It is assumed that α- **thrombin** **activates platelets** by hydrolyzing the **protease** -**activated receptor** (**PAR**)-1, thereby exposing a new N-terminal sequence, a **tethered** ligand, which initiates a cascade of mol. reactions leading to thrombus formation. This process involves crosslinking of adjacent **platelets** mediated by the interaction of **activated glycoprotein** (**GP**) IIb/IIIa with distinct amino acid sequences, LGGAKQAGDV and/or RGD, at each end of dimeric fibrinogen mols. We demonstrate here the existence of a second α- **thrombin**-induced **platelet**-**activating** pathway, dependent on **GP** **Ib**, which does not require hydrolysis of a substrate **receptor**, utilizes polymerizing fibrin instead of fibrinogen, and can be **inhibited** by the Fab fragment of the monoclonal antibody LJIb-10 bound to the **GP Ib thrombin**-binding site or by the cobra venom metalloproteinase, mocarhagin, that hydrolyzes the extracellular portion of **GP Ib.** This alternative α- **thrombin** pathway is observed when **PAR-1** or **GP** IIb/IIIa is **inhibited.** The recognition sites involved in the crosslinking of polymerizing fibrin and surface integrins via the **GP Ib** pathway are different from those associated with fibrinogen. This pathway is insensitive to RGDS and anti-**GP** IIb/IIIa antibodies but reactive with a mutant fibrinogen, γ407, with a deletion of the γ-chain sequence, AGDV. The reaction is not due to simple trapping of **platelets** by the fibrin clot, since ligand binding, signal transduction, and second messenger formation are required. The **GP Ib** pathway is accompanied by mobilization of internal calcium and the **platelet** release reaction. This latter aspect is not observed with ristocetin-induced **GP Ib**-von Willebrand factor agglutination nor with **GP Ib**-von Willebrand factor polymerizing fibrin trapping of **platelets.** Human **platelets** also respond to γ- **thrombin**, an autoproteolytic product of α- **thrombin** , through **PAR-4.** Co-**activation** of the **GP Ib**, **PAR-1**, and **PAR-**

4 pathways elicit synergistic responses. The presence of the **GP Ib** pathway may explain why anti-α-**thrombin**/anti-**platelet** regimens fail to completely abrogate thrombosis/restenosis in the cardiac patient.

ST **thrombin** fibrin polymn calcium **platelet aggregation**

IT Glycolipoproteins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**GPIb**; unique pathway of **thrombin**-induced **platelet aggregation** mediated by **glycoprotein Ib**)

IT **Platelet** (blood)
(**aggregation**; unique pathway of **thrombin**-induced **platelet aggregation** mediated by **glycoprotein Ib**)

IT Fibrins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(in unique pathway of **thrombin**-induced **platelet aggregation** mediated by **glycoprotein Ib**)

IT Cell **aggregation**
(**platelet**; unique pathway of **thrombin**-induced **platelet aggregation** mediated by **glycoprotein Ib**)

IT Molecular association
(unique pathway of **thrombin**-induced **platelet aggregation** mediated by **glycoprotein Ib**)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(release in unique pathway of **thrombin**-induced **platelet aggregation** mediated by **glycoprotein Ib**)

IT **9002-04-4, Thrombin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(unique pathway of **thrombin**-induced **platelet aggregation** mediated by **glycoprotein Ib**)

RE.CNT 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L60 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2001:202249** HCAPLUS
ED Entered STN: 22 Mar 2001
TI Discovery of potent, non-peptide **thrombin receptor antagonists**
AU Chackalamannil, Samuel; Xia, Yan; Clasby, Martin; Greenlee, William; Doller, Dario; Eagen, Keith; Tsai, Hsingan; Asberom, Theodros; Lin, Yan; Czarniecki, Michael; Ahn, Ho-Sam; Foster, Carolyn; Boykow, George
CS CV/CNS Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ, 07033, USA
SO Abstracts of Papers - American Chemical Society (2001), 221st, MEDI-342
CODEN: ACSRAL; ISSN: 0065-7727
PB American Chemical Society
DT Journal; Meeting Abstract
LA English
AB In addition to its key role in hemostasis and wound healing, **thrombin activates** specific cell surface **receptors** known as **protease-activated receptors (PAR)**. **Activation** of **thrombin receptor** stimulates proliferative and proinflammatory processes in a variety of cell types and

may have implications in thrombosis, atherosclerosis, and restenosis. As such, a **thrombin receptor antagonist** may have considerable utility in the treatment of these diseases. Since a **thrombin receptor antagonist** is specific for the cellular actions of **thrombin** and does not interfere with the coagulation cascade, such agents are likely to confer added safety margin with regard to hemorrhagic side effects. Through high throughput **screening**, we have identified 2-iminobenzimidazole derivs. as well as synthetic analogs of the natural product himbacine as **thrombin receptor antagonists.** Systematic SAR studies in these classes of compds. led to **thrombin receptor antagonists** with single digit-nanomolar IC50 values. These compds. **inhibited thrombin** as well as peptide agonist-induced human **platelet aggregation** in a dose-dependent manner.

L60 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2001:202248** HCAPLUS
ED Entered STN: 22 Mar 2001
TI Non-peptidic small molecule **antagonists** of the human **platelet thrombin receptor** (**PAR-1**)
AU Nantermet, Philippe G.; Selnick, Harold G.; Barrow, James C.; Lundell, George F.; Rittle, Kenneth E.; Glass, Kristen L.; Young, MaryBeth; Pellicore, Janetta M.; Ngo, Phung L.; Freidinger, Roger M.; Prendergast, Kris; Condra, Cindra; Karczewski, Jerzy; Gould, Robert; Connolly, Thomas M.
CS Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SO Abstracts of Papers - American Chemical Society (2001), 221st, MEDI-341 CODEN: ACSRAL; ISSN: 0065-7727
PB American Chemical Society
DT Journal; Meeting Abstract
LA English
AB The synthesis and biol. evaluation of a series of non-peptidic small mol. **antagonists** of the human **platelet thrombin receptor** (**PAR-1**) are described. The lead 5-amino-3-arylisoxazole was identified by directed **screening** of the Merck sample collection. Optimization of the lead resulted in an approx. 100 fold increase in potency. The most potent of these compds. display IC50s for the **inhibition** of **platelet activation** in the 100 nM range with the **thrombin receptor** agonist peptide (TRAP) as agonist and also display significant activity when **thrombin** is the agonist.

L60 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2000:796018** HCAPLUS
ED Entered STN: 14 Nov 2000
TI Discovery of a non-peptide small molecule **antagonist** of the human **platelet thrombin receptor** (**PAR-1**).
AU Selnick, Harold; Nantermet, Philippe G.; Rittle, Kenneth; Lundell, George F.; Barrow, James C.; Glass, Kristen; Young, Marybeth; Pellicore, Janetta M.; Ngo, Phung L.; Freidinger, Roger; Prendergast, Kris; Gould, Robert; Condra, Cindra; Karczewski, Jerzy; Connolly, Thomas
CS Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SO Abstracts of Papers - American Chemical Society (2000), 220th, MEDI-021 CODEN: ACSRAL; ISSN: 0065-7727
PB American Chemical Society
DT Journal; Meeting Abstract
LA English
AB Abstract- The synthesis and biol. evaluation of a series of non-peptidic

small mol. **antagonists** of the human **platelet thrombin receptor** (**PAR-1**) are described. The lead 5-(N,N-dialkylamino)-3-phenylisoxazole (1) was identified by directed **screening.** Optimization of the lead resulted in an approx. 200 fold increase in potency. The most potent of these compds. display IC50s for the **inhibition** of **platelet activation** in the 0.1 to 1 uM range with the **thrombin receptor** agonist peptide (TRAP, 3uM) as agonist and also display significant activity when **thrombin** (1 nM) is the agonist. Compds. of this class also **inhibit platelet aggregation** stimulated by **thrombin** (1 nM).

4/27

L60 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1999:728849** HCAPLUS
DN **132:44502**
ED Entered STN: 17 Nov 1999
TI Design, synthesis, and biological characterization of a peptide-mimetic **antagonist** for a **tethered**-ligand **receptor**
AU Andrade-Gordon, Patricia; Maryanoff, Bruce E.; Derian, Claudia K.; Zhang, Han-Cheng; Addo, Michael F.; Darrow, Andrew L.; Eckardt, Annette J.; Hoekstra, William J.; McComsey, David F.; Oksenberg, Donna; Reynolds, Elwood E.; Santulli, Rosemary J.; Scarborough, Robert M.; Smith, Charles E.; White, Kimberly B.
CS Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1999), 96(22), 12257-12262
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 1-3 (Pharmacology)
AB **Protease-activated receptors** (**PARs**) represent a unique family of seven-transmembrane G protein-coupled **receptors**, which are enzymically cleaved to expose a truncated extracellular N terminus that acts as a **tethered activating** ligand. **PAR-1** is cleaved and **activated** by the serine **protease** α-**thrombin**, is expressed in various tissues (e.g., **platelets** and vascular cells), and is involved in cellular responses associated with hemostasis, proliferation, and tissue injury. We have discovered a series of potent peptide-mimetic **antagonists** of **PAR-1**, exemplified by RWJ-56110. Spatial relationships between important functional groups of the **PAR-1** agonist peptide epitope SFLLRN were employed to design and synthesize candidate ligands with appropriate groups attached to a rigid mol. scaffold. Prototype RWJ-53052 was identified and optimized via solid-phase parallel synthesis of chemical libraries. RWJ-56110 emerged as a potent, selective **PAR-1 antagonist**, devoid of **PAR-1** agonist and **thrombin inhibitory** activity. It binds to **PAR-1**, interferes with **PAR-1** calcium mobilization and cellular function (**platelet aggregation**; cell proliferation), and has no effect on **PAR-2**, **PAR-3**, or **PAR-4**. By flow cytometry, RWJ-56110 was confirmed as a direct **inhibitor** of **PAR-1 activation** and internalization, without affecting N-terminal cleavage. At high concns. of α- **thrombin**, RWJ-56110 fully **blocked activation** responses in human vascular cells, albeit not in human **platelets**; whereas, at high concns. of SFLLRN-NH2, RWJ-56110 **blocked activation** responses in both cell types. Thus, **thrombin activates** human **platelets** independently of **PAR-1**,

i.e., through **PAR-4**, which we confirmed by PCR anal. Selective **PAR-1 antagonists**, such as RWJ-56110, should serve as useful tools to study **PARs** and may have therapeutic potential for treating thrombosis and restenosis.

ST peptidomimetic structure **thrombin receptor PAR1 antagonist**

IT **Thrombin receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**PAR-1** (**protease-activated receptor 1**); design, synthesis, and biol. characterization of peptidomimetic **antagonists** for **protease-activated receptor PAR-1**)

IT **Drug design**
Peptidomimetics
Platelet aggregation inhibitors
(design, synthesis, and biol. characterization of peptidomimetic **antagonists** for **protease-activated receptor PAR-1**)

IT Structure-activity relationship
(**receptor**-binding; design, synthesis, and biol. characterization of peptidomimetic **antagonists** for **protease-activated receptor PAR-1**)

IT 252889-86-4P, RWJ 53052 252889-87-5P, RWJ 54399 252889-88-6P, RWJ 56110 252889-89-7P, RWJ 57269
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); BIOL (Biological study); PREP (Preparation)
(design, synthesis, and biol. characterization of peptidomimetic **antagonists** for **protease-activated receptor PAR-1**)

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L60 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1999:640986** HCAPLUS
DN **131:283053**
ED Entered STN: 08 Oct 1999
TI Human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing the **PAR4** ligand
IN Xu, Wen-feng; Presnell, Scott R.; Yee, David P.; Foster, Donald C.
PA Zymogenetics, Inc., USA; University of Washington
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-12
ICS C07K014-705; C07K016-28; A61K038-17
CC 6-3 (General Biochemistry)
Section cross-reference(s): 1, 3, 13
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9950415	A2	19991007	WO 1999-US7100	19990331
	WO 9950415	A3	20000309		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6111075	A	20000829	US 1998-53866	19980401
	AU 9934591	A1	19991018	AU 1999-34591	19990331
	US 6436400	B1	20020820	US 2000-479130	20000107
	US 2003143218	A1	20030731	US 2002-187049	20020628
PRAI	US 1998-53866	A	19980401		
	WO 1999-US7100	W	19990331		
	US 1999-371333	A3	19990810		
	US 2000-479130	A3	20000107		
	US 2000-480720	B3	20000107		

AB The present invention relates to **PAR4**, a novel member of the **protease-activated receptor** family, and DNA encoding it. **PAR4** mediates biol. responses and/or cellular signaling in response to **proteases. Protease** cleavage of **PAR4** exposes a **PAR4** extracellular amino terminal portion that serves as a ligand for the **PAR4 receptor. PAR4** may be used as a target in drug **screening**, and further used to identify proteinaceous or non-proteinaceous **PAR4** agonists and **antagonists.** The present invention also includes antibodies to the **PAR4** polypeptides. A partial cDNA sequence for **PAR4** was identified in an expressed sequence tag database, and the full-length cDNA clone was then isolated from a lymphoma Daudi

cell cDNA library. The ORF codes for a seven transmembrane domain protein of 385 amino acids with 33% amino acid sequence identity with **PAR1**, **PAR2**, and **PAR3**. A putative **protease** cleavage site (Arg-47/Gly-48) was identified within the extracellular amino terminus. COS cells transiently transfected with **PAR4** resulted in the formation of intracellular inositol triphosphate when treated with either **thrombin** or trypsin. A **PAR4** mutant in which Arg-47 was replaced with Ala did not respond to **thrombin** or trypsin. A hexapeptide (GYPGQV) representing the newly exposed **tethered** ligand from the amino terminus of **PAR4** after proteolysis by **thrombin activated** COS cells transfected with either wild-type or the mutant **PAR4**. Northern blot showed that **PAR4** mRNA was expressed in a number of human tissues, with high levels being present in lung, pancreas, thyroid, testis, and small intestine. By fluorescence in situ hybridization, the human **PAR4** gene was mapped to chromosome 19p12.

ST sequence human **protease activated receptor** **PAR4** cDNA

IT Animal cell line
(Daudi; human **protease-activated receptor** **PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT **Receptors**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(**PAR-4** (**proteinase-activated** **receptor 4**); human **protease-** **activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT Lung
Pancreas
Testis
Thyroid gland
(**PAR4** gene expression in; human **protease-** **activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT cDNA sequences
(for human **protease-activated receptor** **4**)

IT Chromosome
(human 19, **PAR4** gene mapped to; human **protease-** **activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT Signal transduction, biological
(human **protease-activated receptor** **PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT Genetic mapping
(of **PAR4** gene to human chromosome 19p12; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT Protein sequences
(of human **protease-activated receptor** **4**)

IT Intestine
(small, **PAR4** gene expression in; human **protease-** **activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT mRNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(tissue distribution of **PAR4**; human **protease-**

activated receptor PAR4 and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT 225779-44-2
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(**PAR4** ligand; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT 98849-88-8 141136-83-6 245652-78-2 245654-44-8 245654-52-8 245654-73-3 245654-80-2
RL: PRP (Properties)
(Unclaimed; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing the **PAR4** ligand)

IT 210413-73-3 210413-76-6 210413-81-3
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(amino acid sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT 245113-08-0 245113-09-1 245113-10-4
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT 210527-54-1
RL: PRP (Properties)
(nucleotide sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT 245739-94-0, PN: WO9950415 SEQID: 3 unclaimed DNA 245739-95-1, PN: WO9950415 SEQID: 9 unclaimed DNA 245739-96-2, PN: WO9950415 SEQID: 10 unclaimed DNA 245739-97-3, PN: WO9950415 SEQID: 11 unclaimed DNA 245739-98-4, PN: WO9950415 SEQID: 12 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing the **PAR4** ligand)

IT 245750-04-3, PN: WO9950415 SEQID: 5 unclaimed protein
RL: PRP (Properties)
(unclaimed protein sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing the **PAR4** ligand)

IT 245740-00-5, PN: WO9950415 PAGE: 6 unclaimed sequence 245740-01-6, PN: WO9950415 PAGE: 6 unclaimed sequence 245740-02-7, PN: WO9950415 PAGE: 6 unclaimed sequence 245740-03-8, PN: WO9950415 PAGE: 6 unclaimed sequence
RL: PRP (Properties)
(unclaimed sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing the **PAR4** ligand)

L60 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1999:566175** HCAPLUS
DN **131:181454**
ED Entered STN: 08 Sep 1999
TI Nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling
IN Coughlin, Shaun R.; Kahn, Mark
PA The Regents of the University of California, USA

SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-12
ICS C07K014-705; C12N009-74; C07K016-28; C12N001-21; C12N001-19; C12N005-10; C12Q001-00; G01N033-68; A61K038-48; A61K038-17
CC 6-3 (General Biochemistry)
Section cross-reference(s): 3, 13, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9943809	A2	19990902	WO 1999-US2983	19990211
	WO 9943809	A3	19991014		
	W: AU, CA, JP, KR, NO				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2321142	AA	19990902	CA 1999-2321142	19990211
	AU 9926728	A1	19990915	AU 1999-26728	19990211
	EP 1056854	A2	20001206	EP 1999-906934	19990211
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002504369	T2	20020212	JP 2000-533549	19990211
	NO 2000004274	A	20001013	NO 2000-4274	20000825
PRAI	US 1998-32397	A	19980227		
	WO 1999-US2983	W	19990211		

AB Disclosed are cDNAs and genomic DNAs encoding **protease-activated receptor 4** (**PAR4**) from mouse and human, and the recombinant polypeptides expressed from such cDNAs. The recombinant **receptor** polypeptides, **receptor** fragments and analogs expressed on the surface of cells are used in methods of **screening** candidate compds. for their ability to act as agonists or **antagonists** to the effects of interaction between **thrombin** and **PAR4.** Agonists are used as therapeutics to treat wounds, promote clotting, and as reagents to **activate platelets** in diagnostic tests. **Antagonists** are used as therapeutics to control blood coagulation, treat heart attack and stroke, and **block** inflammatory and proliferative responses to injury as occur in normal wound healing and variety of diseases including atherosclerosis, restenosis, pulmonary inflammation (ARDS) and glomerulosclerosis. Antibodies specific for a **protease-activated receptor 4** (or **receptor** fragment or analog) and their use as a therapeutic are also disclosed.

ST **protease activated receptor 4** cDNA sequence human; **thrombin** signaling **protease activated receptor 4**

IT Drugs
(agonists/**antagonists**; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT Antiarteriosclerotics
(antiatherosclerotics; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT Heart, disease
(attack, treatment of; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT Molecular cloning
(expression system; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT **Drug screening**

(for agonists/**antagonists**; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT cDNA sequences
(for human and murine **protease-activated receptor PAR-4**)

IT Lung, disease
(inflammation, treatment of; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT **Anticoagulants**
Coagulants
Wound healing promoters
(nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT Antibodies
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT Protein sequences
(of human and murine **protease-activated receptor PAR-4**)

IT DNA sequences
(of murine **protease-activated receptor PAR-4** gene intron **1**)

IT **Cell aggregation**
(**platelet**; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT Artery, disease
(restenosis, treatment of; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT Brain, disease
(stroke, treatment of; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT Megakaryocyte
Spleen
(tissue expression specific for; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT **9002-04-4**, **Thrombin** 9002-07-7, Trypsin 164081-25-8 213018-42-9 225779-44-2 239076-98-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**activation** by; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT 210413-73-3 213124-64-2
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(amino acid sequence; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α- **thrombin** signaling)

IT 177872-36-5, GenBank W75830
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(isolation of murine cDNA using; nucleic acids encoding human and

murine **protease-activated receptor** **4** and their uses in α- **thrombin** signaling)

IT 212277-59-3 239124-21-1 239124-23-3
RL: ANT (Analyte); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; nucleic acids encoding human and murine **protease-activated receptor** **4** and their uses in α- **thrombin** signaling)

IT 239077-05-5 239077-06-6 239077-07-7 239077-52-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(peptide **antagonist**; nucleic acids encoding human and murine **protease-activated receptor** **4** and their uses in α- **thrombin** signaling)

9/27

L60 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1999:314936** HCAPLUS
DN **131:124796**
ED Entered STN: 24 May 1999
TI **Proteinase-activated tethered** ligand **receptors** (**PARs**): novel targets for drug development
AU Hollenberg, Morley D.
CS Endocrine, Smooth Muscle and Cancer Biology Research Groups Department of Pharmacology & Therapeutics and Department of Medicine University of Calgary, Faculty of Medicine, Calgary, AB, T2N 4N1, Can.
SO Biomedical and Health Research (1999), 22(Bioactive Peptides in Drug Discovery and Design: Medical Aspects), 265-274
CODEN: BIHREN; ISSN: 0929-6743
PB IOS Press
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 13
AB A review with 58 refs. The search for the **thrombin** **receptor** led to the discovery of a **proteinase-activated** G-protein-coupled **receptor** (**PAR1**) that is **activated** by a **tethered**-ligand mechanism. Because short peptides based on the **tethered** ligand sequence of **PAR1** can, in isolation, **activate** **PAR1**, considerable effort has gone into the study of the structure-activity relationships for the **receptor-activating** peptides (**PAR**-APs). Shortly after the description of **PAR1**, two new **proteinase-activated** **receptors** were discovered, one (**PAR2**) **activated** by trypsin, but not **thrombin**; and another (**PAR3**), **activated** preferentially by **thrombin.** Reports of the discovery of yet another **thrombin-activated** **receptor** (**PAR4**) have also been published. The amino acid sequences of the **tethered** **activating** ligands for the human **receptors** are: SFLLRN...(**PAR1**); SLIGKV...(**PAR2**), TFRGAP...(**PAR3**) and GYPGQV...(**PAR4**). Structure-activity studies for the differential **activation** of the different **PARs** by these **tethered** ligand sequences has revealed a complex cross-reactivity of the **PAR**-APs for the different **receptors.** Further, pharmacol. data obtained with the **PAR**-APs point to the existence of a more extended **receptor** superfamily for which not all members have yet been cloned. This situation bears directly on the development of **PAR**-selective agonists and **antagonists** that may prove of therapeutic utility.
ST review **proteinase** **receptor** drug development target
IT G protein-coupled **receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(**PAR** (**proteinase-activated receptor**); **proteinase-activated tethered** ligand **receptors** (**PARs**) as novel targets for drug development)
IT Structure-activity relationship
(**proteinase-activated receptor**-affecting; **proteinase-activated tethered** ligand **receptors** (**PARs**) as novel targets for drug development)
IT **Drug design**
Pharmacodynamics
(**proteinase-activated tethered** ligand **receptors** (**PARs**) as novel targets for drug development)
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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(5) Blackhart, B; J Biol Chem 1996, V271, P16466 HCAPLUS
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(35) Zheng, X; J Pharmacol Exp Ther 1998, V285, P325 HCAPLUS
(36) Zhong, C; J Biol Chem 1992, V267, P16975 HCAPLUS

L60 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1998:293364** HCAPLUS
DN **129:12725**
ED Entered STN: 20 May 1998
TI **Protease-activated receptor 3** and therapeutic uses thereof
IN Coughlin, Shaun R.; Ishihara, Hiroaki; Connolly, Andrew

PA Regents of the University of California, USA
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
ICS A61K035-00; A61K038-00; C07K014-435; C07K014-705; C12N005-10; C12N015-12; C12N015-63; G01N033-53; G01N033-566
CC 1-1 (Pharmacology)
Section cross-reference(s): 9, 15
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9818456	A1	19980507	WO 1997-US19732	19971029 <--
	W: CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5892014	A	19990406	US 1996-742440	19961030 <--
	EP 948323	A1	19991013	EP 1997-946388	19971029 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001510988	T2	20010807	JP 1998-520768	19971029 <--
PRAI	US 1996-742440	A	19961030 <--		
	WO 1997-US19732	W	19971029 <--		

AB Disclosed are cDNAs and genomic DNAs encoding **protease-activated receptor 3** (**PAR3**) from mouse and human, and the recombinant polypeptides expressed from such cDNAs. The recombinant **receptor** polypeptides, **receptor** fragments and analogs expressed on the surface of cells are used in methods of **screening** candidate compds. for their ability to act as agonists or **antagonists** to the effects of interaction between **thrombin** and **PAR3**. Agonists are used as the therapeutics to treat wounds, thrombosis, atherosclerosis, restenosis, inflammation, and other **thrombin-activated** disorders. **Antagonists** are used as therapeutics to control blood coagulation and thereby treating heart attack and stroke. **Antagonists** mediate inflammatory and proliferative responses to injury as occur in normal wound healing and variety of diseases including atherosclerosis, restenosis, pulmonary inflammation (ARDS) and glomerulosclerosis. Antibodies specific for a **protease-activated receptor 3** (or **receptor** fragment or analog) and their use as a therapeutic are also disclosed.

ST **protease activated receptor 3** modulator sequence

IT **Receptors**
RL: PRP (Properties)
(**PAR-3** (**proteinase-activated receptor 3**); **protease-activated receptor 3** and therapeutic uses thereof)

IT Drug delivery systems
(carriers; **protease-activated receptor 3** and therapeutic uses thereof)

IT Phosphoinositides
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hydrolysis of; **protease-activated receptor 3** and therapeutic uses thereof)

IT Bioassay
Blood coagulation
DNA sequences
Drug screening
Genetic vectors
Molecular cloning
Platelet aggregation inhibitors

Protein sequences
cDNA sequences
(**protease-activated receptor 3**
and therapeutic uses thereof)

IT 207754-23-2P 207754-26-5P
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); USES (Uses)
(amino acid sequence; **protease-activated receptor 3** and therapeutic uses thereof)

IT 207754-21-0P 207754-22-1P 207754-24-3P 207754-25-4P
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(nucleotide sequence; **protease-activated receptor 3** and therapeutic uses thereof)

IT 207461-57-2 207461-58-3 207461-59-4 207461-60-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**protease-activated receptor 3** and therapeutic uses thereof)

IT **9002-04-4, Thrombin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proteins **activated** by; **protease-activated receptor 3** and therapeutic uses thereof)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Coleman; US 5686597 A 1997 HCAPLUS
(2) Coughlin; US 5256766 A 1993 HCAPLUS
(3) Ishihara; Nature 1997, V386, P502 HCAPLUS
(4) Nystedt; Proc Natl Acad Sci USA 1994, V91, P9208 HCAPLUS

L60 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1997:43728** HCAPLUS
DN **126:142434**
ED Entered STN: 20 Jan 1997
TI A possible dual physiological role of extracellular ATP in the modulation of **platelet aggregation**
AU **Soslau, Gerald**; Youngprapakorn, Donya
CS Department of Biochemistry, Medical College of Pennsylvania and Hahnemann University, Philadelphia, PA, 19102-1192, USA
SO Biochimica et Biophysica Acta (1997), 1355(2), 131-140
CODEN: BBACAQ; ISSN: 0006-3002
PB Elsevier
DT Journal
LA English
CC 13-5 (Mammalian Biochemistry)
AB ATP and ADP are simultaneously released from **activated platelets** in equimolar concns. Micromolar concns. of ATP **inhibit platelet aggregation** by both competitive and non-competitive mechanisms. The current studies addressed the question of how **platelets** respond to agonists in the presence of nanomolar and micromolar concns. of ATP and ADP alone or in combination. This is a significant issue since the concentration of ATP±ADP may vary widely within a microenvironment depending upon the source and cause for the release of the nucleotides. ATP (1-10 nM) was found to significantly enhance the thromboxane A2 analog, U44619-, collagen- and **thrombin**-induced **platelet aggregations.** Conversely, ATP at 1-100 μM **inhibited** these same reactions. ADP, in general, behaved exactly opposite to ATP. When equal amts. of ATP and ADP were added together the ADP response appeared to predominate. The

observed ATP-induced response was not due to a hydrolytic product as evidenced by an unaltered response to ATP in the presence of adenosine deaminase or the ATP generating system, creatine phosphate plus creatine phosphokinase. Adenosine (1-10 nM), like ADP, **inhibited** agonist-induced **platelet aggregation.** The stimulation of agonist-induced **platelet aggregation** by 1-10 nM extracellular ATP appears to depend upon the phosphorylation of **platelet** membrane ecto proteins. The ATP analog, βγ-methylene ATP, that is incapable of serving as a phosphate donor for protein kinases, **inhibited** rather than stimulated agonist-induced **platelet aggregation.** The dual response of **platelets** to low and high concns. of extracellular ATP±ADP may play a physiol. role in hemostasis and thrombosis under normal and pathol. conditions.

ST ATP ADP phosphorylation **platelet aggregation**

IT **Platelet** (blood)
(**aggregation**; possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT Cell **aggregation**
(**platelet**; possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT Phosphorylation, biological
(possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT Collagens, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT 56-65-5, 5'-ATP, biological studies 58-64-0, 5'-ADP, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT 58-61-7, Adenosine, biological studies **9002-04-4**, **Thrombin** 56985-40-1, U46619
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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4/17

L60 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1995:310801** HCAPLUS
DN **122:122390**
ED Entered STN: 24 Jan 1995
TI Identification of novel peptide **antagonists** for von Willebrand factor binding to the **platelet glycoprotein Ib receptor** from a phage epitope library
AU South, Victoria; Searfoss, George H.; French, Stephen; Cheadle, Christopher; Murray, Edward; Howk, Richard; Jaye, Michael; Ricca, George A.
CS Dep. Molecular Biol., Rhone-Poulenc Rorer Central Res., Collegeville, PA, USA
SO Thrombosis and Haemostasis (**1995**), 73(1), 144-50
CODEN: THHADQ; ISSN: 0340-6245
PB Schattauer
DT Journal
LA English
CC 1-1 (Pharmacology)
Section cross-reference(s): 3
AB The authors have constructed a fusion phage epitope library in the filamentous bacteriophage fuse5. The library was made by inserting a degenerate oligonucleotide which encodes 15 variable amino acids into the NH2-terminal region of the phage gene III protein. This library, containing over 107 different epitope bearing phage, has been used to identify **inhibitors** of the von Willebrand factor (vWF)-**platelet Glycoprotein Ib** interaction. The library was **screened** with a monoclonal antibody (RG46) that recognized the **GPIb** binding domain of vWF (amino acids 445-733). A total of 30 clones falling into 8 classes have been identified that react with the RG46 antibody. Isolates from all 8 classes are pos. by immunoblot anal. The amino acid sequence of the gene III fusion protein from pos. clones showed a strong homol. to the known RG46 epitope. Peptides identified from the **screen** were synthesized and used to demonstrate that some of the synthetic peptides exhibited **inhibitory** activity towards ristocetin induced binding of vWF to the **GPIb receptor.** Thus, the authors have demonstrated that **screening** a fusion phage epitope library with a monoclonal antibody that **inhibits** vWF binding to the **GPIb receptor** can be a useful tool not only for mapping antibody recognizing determinants, but also can serve as a source for identifying novel peptides that are **antagonists** for vWF binding to the **platelet GPIb receptor.**
ST peptide **antagonist** von Willebrand factor; **glycoprotein** von Willebrand factor binding **antagonist**; epitope library **screening antithrombotic**
IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(identification of novel peptide **antagonists** for von Willebrand factor binding to **platelet glycoprotein Ib receptor** from a phage epitope library)

IT **Anticoagulants and Antithrombotics**
(identification of potential **antithrombotic** peptides by **screening** a fusion phage epitope library with a monoclonal antibody that **inhibits** von Willebrand factor binding)

IT Glycolipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**GPIb**, complexes, identification of novel peptide **antagonists** for von Willebrand factor binding to **platelet glycoprotein Ib receptor** from phage epitope library)

IT 160951-87-1 160951-88-2 160951-89-3 160951-90-6 160951-91-7
160951-92-8 160951-93-9 160951-94-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(identification of novel peptide **antagonists** for von Willebrand factor binding to **platelet glycoprotein Ib receptor** from a phage epitope library)

IT **109319-16-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(identification of novel peptide **antagonists** for von Willebrand factor binding to **platelet glycoprotein Ib receptor** from a phage epitope library)

L60 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1993:617409** HCAPLUS
DN **119:217409**
ED Entered STN: 27 Nov 1993
TI Analogs of von Willebrand factor-binding peptides of **glycoprotein GPIb**.alpha. and their manufacture for use as **antithrombotics**
IN Ruggeri, Zaverio M.; Ware, Jerry L.
PA Scripps Research Institute, USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K037-00
ICS A61K039-00; C07H015-12; C07H017-00; C07K003-00; C07K013-00; C07K015-00; C07K017-00
CC 1-8 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9316712	A1	19930902	WO 1993-US1734	19930225 <--
	W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
	AU 9337347	A1	19930913	AU 1993-37347	19930225 <--
PRAI	US 1992-842077		19920226 <--		
	WO 1993-US1734		19930225 <--		

AB Peptides derived from **glycoprotein GPIb**.alpha. sequences that interact with von Willebrand factor are prepared for use as **antithrombotics**. These peptides have amino acid substitutions

that increase their affinity for von Willebrand factor. The peptides are manufactured by expression of the coding sequence in an appropriate host. An analog of His1-Ala302 **glycoprotein GP1.**alpha. with Gly-233 was prepared by site-directed mutagenesis of the gene and the protein manufactured by expression in CHO-KI cells. Ristocetin-induced binding of 125I-von Willebrand factor to the novel peptide was measured by an enzyme-linked immunofiltration technique using conditioned medium as a source of the **glycoprotein.** The novel peptide showed binding to von Willebrand factor comparable to the wild type at high ristocetin concns. but the analog more efficient binding at low ristocetin concns. Methods for mutagenesis and **screening** for peptides with increased affinity are described.

ST **glycoprotein GPIbalpha** analog von Willebrand factor

IT Blood **platelet**
(**activation** and adhesion **inhibitors** for, **glycoprotein GPIb.**alpha. fragments and analogs with increased binding to von Willebrand factor as)

IT Gene, animal
RL: BIOL (Biological study)
(cDNA, for amino acid-substituted **glycoprotein GPIb** α N-terminal fragment, expression in animal cell culture of)

IT **Anticoagulants and Antithrombotics**
Blood platelet aggregation inhibitors
(**glycoprotein GPIb.**alpha. fragments and analogs with increased binding to von Willebrand factor as)

IT Plasmid and Episome
(pMW1, cDNA for **glycoprotein GPIb.**alpha. on, expression in animal cell culture of)

IT Plasmid and Episome
(pMW2, cDNA for **glycoprotein GPIb.**alpha. N-terminal fragment on, expression in animal cell culture of)

IT Plasmid and Episome
(pMW2/G233V, cDNA for amino acid-substituted **glycoprotein GPIb.**alpha. N-terminal fragment on, expression in animal cell culture of)

IT Antibodies
RL: BIOL (Biological study)
(to **glycoprotein GPIb.**alpha. fragments and analogs binding to von Willebrand factor)

IT Glycolipoproteins
RL: BIOL (Biological study)
(**GPIb**, **GPIb.**alpha., fragments of, analogs of, with increased affinity for von Willebrand factor)

IT 72-18-4, Valine, biological studies
RL: BIOL (Biological study)
(amino acid substitution in **glycoprotein GPIb** α with, in preparation analogs with increased affinity for von Willebrand factor)

IT **109319-16-6**
RL: BIOL (Biological study)
(**glycoprotein GPIb.**alpha. fragment analogs with increased affinity for)

IT 56-40-6, Glycine, biological studies 63-68-3, Methionine, biological studies
RL: BIOL (Biological study)
(substitution in **glycoprotein GPIb.**alpha. of, in preparation analogs with increased affinity for von Willebrand factor)

L60 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1992:443844** HCAPLUS
DN **117:43844**
ED Entered STN: 08 Aug 1992
TI The bioluminescent detection of **platelet** released ATP:

collagen-induced release and potential errors
AU **Soslau, Gerald**; Parker, Janet
CS Med. Sch., Hahnemann Univ., Philadelphia, PA, 19102-1192, USA
SO Thrombosis Research (1992), 66(1), 15-21
CODEN: THBRAA; ISSN: 0049-3848
DT Journal
LA English
CC 9-5 (Biochemical Methods)
Section cross-reference(s): 13
AB The bioluminescent detection of ATP released from **activated platelets** is an important diagnostic and exptl. assay. Potential errors in the interpretation of the data may be introduced due to the lability of luciferin-luciferase and the amount of **platelet** agonist employed. Loss of luciferin-luciferase activity is temperature dependent with a 50% decrease in activity in 1-4 min at 37°. Plasma components do not appear to contribute to the inactivation of the detection system. Due to the significant loss of enzyme activity at variable times, the method of standardizing ATP concns. is crucial for the accurate determination of ATP released from **activated platelets**. A nearly 5-fold error is introduced into the routinely employed assay procedure where the standard ATP concentration is determined 5 min after the addition of agonist. This report demonstrates that the standard ATP concentration must be determined with a sep. **platelet** sample at the same time as the ATP was released from the agonist-induced exptl. **platelet** sample. A second significant error in the assay system may be introduced by the agonist concentration employed even when the final level of **aggregation** is the same. When collagen is employed as the agonist the amount of ATP released appears to depend, in **part**, on the initial intensity of the **aggregation** response and not on collagen type (Type I vs. IV). The corrective procedures described here for the detection of ATP are not likely to change the qual. results of most studies but would significantly alter the quant. results.
ST ATP release **platelet** detn bioluminescence collagen
IT Blood **platelet**
(ATP release from, of human, factors affecting bioluminescent determination of)
IT Collagens, uses
RL: USES (Uses)
(type I, ATP determination following release from human blood **platelets** by bioluminescent assay response to)
IT Collagens, uses
RL: USES (Uses)
(type IV, ATP determination following release from human blood **platelets** by bioluminescent assay response to)
IT **9002-04-4, Thrombin**
RL: ANST (Analytical study)
(ATP determination following release from human blood **platelets** by bioluminescent assay response to)
IT 56-65-5, 5'-ATP, analysis
RL: ANT (Analyte); ANST (Analytical study)
(determination of, released from human blood **platelet**, factors affecting bioluminescent method for)
IT 2591-17-5, Luciferin 9014-00-0, Luciferase
RL: ANST (Analytical study)
(in ATP determination from human blood **platelets**, factors affecting)

=> => fil biosis
FILE 'BIOSIS' ENTERED AT 07:12:26 ON 09 MAR 2004

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 3 March 2004 (20040303/ED)

FILE RELOADED: 19 October 2003.

=> d all tot l65

L65 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN **2003:335571** BIOSIS
DN **PREV200300335571**
TI (Xi)Melagatran Inhibition of Alpha-Thrombin-Gp Ib and Beta-, Gamma-Thrombin-Par-4 Platelet Aggregation Pathways.
AU **Soslau, Gerald** [Reprint Author]; Goldenberg, Seth J. [Reprint Author]; Navas, Edgar [Reprint Author]; Mattsson, Christer [Reprint Author]; Nylander, Sven [Reprint Author]
CS Biochemistry, Drexel University College of Medicine, Philadelphia, PA, USA
SO Blood, (November 16 2002) Vol. 100, No. 11, pp. **Abstract** No. 971. print.
Meeting Info.: **44th Annual Meeting of the American Society of Hematology.** Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT **Conference; (Meeting)**
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 23 Jul 2003
Last Updated on STN: 22 Aug 2003
AB Melagatran is the active form of ximelagatran, an oral direct thrombin inhibitor, which has been shown to interact directly with alpha-thrombin. Clinical trials have shown ximelagatran to be as efficacious as warfarin without requiring routine coagulation monitoring. Thrombin plays a major role in the regulation of hemostasis and thrombosis. Therefore, the ability to regulate this proteolytic enzyme is of great clinical significance. Unfortunately, there are multiple active forms of thrombin that: differentially activate several receptor types; react with a variety of substrates, and; are differentially sensitive to inhibitors. To date, no one drug inhibits all thrombin-linked pathways. It is critical to evaluate each potential antithrombotic drug to determine if it involves new, overlapping or synergistic inhibitory activities with current drug therapies. Methods: Preclinical coagulation studies have been extended to evaluate the in vitro effect of melagatran on alpha-, beta-, and gamma-thrombin activities with peptide substrates and human platelet-induced aggregation at the GP Ib, PAR-1and PAR-4 thrombin receptors. Alpha-thrombin activates GP Ib and PAR-1, beta- and gamma-thrombin activate PAR-4. The final melagatran concentration was varied between 3.75nM to 3.75uM. Results: At 37.5nM and 375nM melagatran significantly inhibits the alpha-thrombin hydrolysis of a small thrombin specific peptide substrate while beta- and gamma-thrombin are marginally affected. Platelets that have been preincubated for 10 min at 37 C with a final concentration of 3.75nM melagatran became virtually unresponsive to alpha-, beta- or gamma-thrombin. PAR-1 was not affected since TRAP-1 (SFLLRNP) induced a full platelet aggregation response. GP Ib and PAR-4 thrombin receptors were inhibited by melagatran. This is evidenced by a lack of aggregatory response to alpha-thrombin with PAR-1 and PAR-4 inactivated platelets while these same inactivated platelet preparations aggregated fully in the absence of melagatran via the GP Ib pathway. No response to TRAP-4A (AYPGKF) was observed with platelets preincubated only with melagatran. The receptor-drug interaction appears to be reversible since increasing the agonist levels could overcome the inhibition.

Conclusion: Melagatran appears to target thrombin activated pathways not affected by other commonly employed antithrombotics and may be very important in combination therapies.

CC **General biology - Symposia, transactions and proceedings 00520**
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Blood and hematopoietic agents 22008
Pharmacology - Cardiovascular system 22010

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Pharmacology

IT Parts, Structures, & Systems of Organisms
platelet: blood and lymphatics, aggregation

IT Chemicals & Biochemicals
(Xi)melagatran: antithrombotic-drug, cardiovascular-drug, hematologic-drug; PAR-1 [protease-activated receptor-1]: regulation; PAR-4 [protease-activated receptor-4]: regulation; TRAP-1 [thrombin receptor activating peptide for protease-activated receptor-1]; alpha-thrombin; alpha-thrombin-Gp Ib: regulation; beta-thrombin; gamma-thrombin

IT Miscellaneous Descriptors
drug synergistic inhibitory activity

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 192939-46-1 ((Xi)melagatran)
9002-04-4 (alpha-thrombin)
9002-04-4 (beta-thrombin)
9002-04-4 (gamma-thrombin)

L65 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN **2003:335570** BIOSIS
DN **PREV200300335570**
TI Differential Activation and Inhibition of Human Platelet Thrombin Receptors by Structurally Distinct Alpha-, Beta- and Gamma-Thrombins.
AU **Soslau, Gerald** [Reprint Author]; Goldenberg, Seth J. [Reprint Author]; Class, Reiner [Reprint Author]; Jameson, Bradford [Reprint Author]
CS Biochemistry, Drexel Univ Coll of Medicine, Phila, PA, USA
SO Blood, (November 16 2002) Vol. 100, No. 11, pp. **Abstract** No. 970. print.
Meeting Info.: **44th Annual Meeting of the American Society of Hematology.** Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT **Conference; (Meeting)**
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 23 Jul 2003
Last Updated on STN: 22 Aug 2003
AB The development of drugs to neutralize the action of thrombin has to date focused on the alpha form of the protease. It is generally agreed that inactive prothrombin is proteolytically converted to active alpha-thrombin which may be further hydrolyzed to beta- and gamma-thrombin. While all three forms of the enzyme retain catalytic activities only alpha-thrombin

is presumed to be physiologically important. The beta- and gamma-thrombin are presumed to be degradation products of no physiological significance. Our demonstration that beta- and gamma-thrombin selectively activate PAR-4 in this and a previous report (J. Biol. Chemical 276, 21173-21183, 2001) necessitates a reevaluation of how we view their physiological role and how we approach the pharmacological regulation of their actions. beta-Thombin, like gamma-thrombin, at nM levels selectively activates PAR-4. This was demonstrated by full retention of aggregatory activity with platelets whose PAR-1 and GP Ib receptors were inactivated. Furthermore, the beta-thombin response was abrogated by desensitizing platelets with suboptimal levels of the thrombin receptor activating peptide for PAR-4 (TRAP-4). alpha-Thrombin is rapidly converted to beta- and gamma-thrombin by activated factor X at physiological pH, in vitro. This implies that the same may hold true in vivo in the proper microenvironment. The differential activation of the three platelet thrombin receptors by alpha-, beta- and gamma-thrombin implies selective structural variations between these thrombin species. This would also account for the marked differential response to the antithrombotics, heparin and hirudin, which are found to be poor inhibitors of beta- and gamma-thrombin-induced platelet aggregation. Histone-1 selectively inhibits beta- and gamma-thrombin with no effect on alpha-thrombin. However, histone-1 appears to function primarily at the receptor level of PAR-4 rather than on the thrombin molecule. Since trypsin, like beta- and gamma-thrombin, activates PAR-4 and is also inactive with TRAP-4 desensitized platelets it was hypothesized that the crystalline structure of gamma-thrombin would be more like that of trypsin than alpha-thrombin. The analysis of the crystalline structures of alpha-, gamma-thrombin and trypsin confirm that this is the case. It is further postulated that the physiologic activator of PAR-2 may be beta- and gamma-thrombin since it, like PAR-4, can be activated by trypsin. These findings should help to elucidate structure-function relationships of the different thrombins and may aid in the development of new antithrombotic drugs.

CC **General biology - Symposia, transactions and proceedings 00520**
Biochemistry studies - Carbohydrates 10068
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Pharmacology - General 22002
Pharmacology - Blood and hematopoietic agents 22008
Pharmacology - Cardiovascular system 22010

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Pharmacology

IT Parts, Structures, & Systems of Organisms
platelet: blood and lymphatics, aggregatory activity

IT Chemicals & Biochemicals
GP Ib receptor [glycoprotein Ib receptor]: regulation; PAR-1 [protease-activated receptor-1]: regulation; PAR-4 [protease-activated receptor-4]: regulation; alpha-thrombin: catalytic activity, structural variation; beta-thrombin: catalytic activity, structural variation; factor X: regulation; gamma-thrombin: catalytic activity, structural variation; heparin: antithrombotic-drug, cardiovascular-drug, hematologic-drug; hirudin: antithrombotic-drug, cardiovascular-drug, hematologic-drug; histone-1; thrombin receptor: regulation; thrombin receptor activating peptide for protease-activated receptor-4 [TRAP-4]; trypsin [EC 3.4.21.4]: crystalline structure

IT Miscellaneous Descriptors
structure-function relationship

RN 9002-04-4 (alpha-thrombin)
9002-04-4 (beta-thrombin)
9001-29-0 (factor X)
9002-04-4 (gamma-thrombin)
9005-49-6 (heparin)

8001-27-2 (hirudin)
9002-07-7 (trypsin)
9002-07-7 (EC 3.4.21.4)

L65 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN **2001:255186** BIOSIS
DN **PREV200100255186**
TI The three thrombin receptors on human platelets respond differentially to alpha-, beta-, and gamma-thrombin.
AU **Soslau, Gerald** [Reprint author]; Goldenberg, Seth J. [Reprint author]; Class, Reiner [Reprint author]
CS MCPHahnemann Univ, 245 N 15th Street, Philadelphia, PA, 19102-1192, USA
SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A896. print.
Meeting Info.: **Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001.** Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DT **Conference; (Meeting)**
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002
AB Cardiovascular diseases remain the leading cause of death in the USA despite the availability of clinically employed anti-thrombotic and anti-platelet drugs. The presumption that alpha-thrombin and the platelet fibrinogen receptor, GP IIb/IIIa, are the two targets in coagulation and platelet aggregation pathways that need to be inhibited to fully regulate hemostasis and thrombosis needs to be revisited. We have found that the controversially defined thrombin receptor, GP Ib, is activated by alpha-thrombin via a pathway that is insensitive to GP IIb/IIIa inhibitors. The GP Ib pathway is readily detected when PAR-1 is blocked. Aggregation under these conditions is inhibited by the anti-GP Ib antibody, LJ Ib-10, or by the cobra venom metalloproteinase, mocarhagin, that hydrolyzes off the extracellular portion of GP Ib. Furthermore, three active forms of thrombin exist with alpha-thrombin being the major player, however, the two actoproteolytic products, beta- and gamma-thrombin are potentially significant contributors to hemostasis as well. These three thrombins function differentially at the three platelet thrombin receptors, GP Ib, PAR-1 and PAR-4, and also respond differently to thrombin inhibitors. At 0.1-10nM levels of thrombins, PAR-4 can only be activated by gamma-thrombin while GP Ib and PAR-1 are insensitive to gamma-thrombin, but both respond to alpha-thrombin. Beta-thrombin appears to be more selective for PAR-1. Gamma-thrombin/PAR-4 is inhibited stoichiometrically by histone-1 while alpha- and beta-thrombins and their receptors are insensitive. The three thrombin species display different sensitivities to heparin. Gamma-thrombin is totally insensitive to hirudin while alpha- and beta-thrombins are completely inhibited. These thrombin species can function synergistically and some individuals also appear to possess varying levels of the three thrombin receptors. It is likely that these disparate properties along with differential responses to drugs could account for continued coronary disease processes even in the light of aggressive therapy regimens.
CC Blood - Blood and lymph studies 15002
General biology - Symposia, transactions and proceedings 00520
Cardiovascular system - Blood vessel pathology 14508
Blood - Blood cell studies 15004
IT Major Concepts
Blood and Lymphatics (Transport and Circulation)
IT Parts, Structures, & Systems of Organisms
platelet: blood and lymphatics
IT Diseases
cardiovascular disease: vascular disease
Cardiovascular Diseases (MeSH)

IT Diseases
thrombosis: vascular disease
Thrombosis (MeSH)
IT Chemicals & Biochemicals
LJ Ib-10: anti-GP Ib antibody inhibitor; alpha-thrombin; beta-thrombin; gamma-thrombin; mocarhagin: anti-GP Ib antibody inhibitor, cobra venom metalloproteinase; thrombin receptors
IT Miscellaneous Descriptors
hemostasis; **Meeting Abstract**
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 171040-76-9 (mocarhagin)

L65 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN **1998:67560** BIOSIS
DN **PREV199800067560**
TI Aggregation of human platelets and megakaryocyte-like cells (HU3) induced by a non-RGDS fibrin, non-proteolytic thrombin-GPIb pathway.
AU **Soslau, G.** [Reprint author]; Morgan, D. A.; Class, R.; Brodsky, I.; Marchese, P.; Ruggeri, Z. M.
CS Allegheny Univ. Health Sci., Philadelphia, PA, USA
SO Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 284A. print.
Meeting Info.: **39th Annual Meeting of the American Society of Hematology.** San Diego, California, USA. December 5-9, 1997. The American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT **Conference; (Meeting)**
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 30 Jan 1998
Last Updated on STN: 30 Jan 1998
CC Blood - General and methods 15001
Cytology - General 02502
Biochemistry studies - General 10060
Cardiovascular system - General and methods 14501
General biology - Symposia, transactions and proceedings 00520
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cardiovascular System (Transport and Circulation); Cell Biology
IT Parts, Structures, & Systems of Organisms
platelet: blood and lymphatics, aggregation
IT Diseases
atherosclerosis: vascular disease
Arteriosclerosis (MeSH)
IT Chemicals & Biochemicals
fibrin: non-RGDS; fibrinogen; hirudin; thrombin; thrombin-GPIb [thrombin-glycoprotein Ib]: pathway; SFLLRNP: thrombin receptor activating peptide; 7 transmembrane thrombin receptor [7TMTR]
IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
HU3: megakaryocyte-like cells

Taxa Notes
Animals
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 8001-27-2 (hirudin)
9002-04-4 (thrombin)

L65 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN **1997:53080** BIOSIS
DN **PREV199799352283**
TI GPIb is a slow response thrombin receptor detectable in human platelets and cultured cells independent of a rapid thrombin response.
AU **Soslau, G.**; Morgan, D. A.; Brodsky, I.; Class, R.
CS Allegheny Univ. Health Sci., Philadelphia, PA, USA
SO Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 25A.
Meeting Info.: **Thirty-eighth Annual Meeting of the American Society of Hematology.** Orlando, Florida, USA. December 6-10, 1996.
CODEN: BLOOAW. ISSN: 0006-4971.
DT **Conference; (Meeting)**
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 4 Feb 1997
Last Updated on STN: 5 Feb 1997
CC **General biology - Symposia, transactions and proceedings 00520**
Cytology - Human 02508
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Membrane phenomena 10508
Enzymes - Physiological studies 10808
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
In vitro cellular and subcellular studies 32600
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology)
IT Chemicals & Biochemicals
THROMBIN
IT Miscellaneous Descriptors
BLOOD AND LYMPHATICS; GPIB PROTEIN; HEMOSTASIS; HU3 CELL LINE; PLATELET ACTIVATION; RAPID RESPONSE; SLOW RESPONSE THROMBIN RECEPTOR; THROMBIN; THROMBOSIS
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 9002-04-4 (THROMBIN)

L65 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN **1996:51314** BIOSIS
DN **PREV199698623449**
TI Typical and atypical platelet-like responses to thrombin and ATP by HU3, a human megakaryocytic (MEG) cell line.

AU **Soslau, G.** [Reprint author]; Morgan, D. A.; Brodsky, I.
CS Med. Coll. of Pa., Philadelphia, PA, USA
SO Blood, (1995) Vol. 86, No. 10 SUPPL. 1, pp. 909A.
Meeting Info.: **37th Annual Meeting of the American Society of Hematology.** Seattle, Washington, USA. December 1-5, 1995.
CODEN: BLOOAW. ISSN: 0006-4971.
DT **Conference; (Meeting)**
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 2 Feb 1996
Last Updated on STN: 3 Feb 1996
CC **General biology - Symposia, transactions and proceedings 00520**
Cytology - Human 02508
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Minerals 10069
Enzymes - Physiological studies 10808
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Lymphatic tissue and reticuloendothelial system 15008
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
THROMBIN; ATP; CALCIUM
IT Miscellaneous Descriptors
CALCIUM; FIBRINOGEN; **MEETING ABSTRACT**; PLATELET AGGREGATION
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Hominidae
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 9002-04-4 (THROMBIN)
56-65-5Q (ATP)
42530-29-0Q (ATP)
94587-45-8Q (ATP)
111839-44-2Q (ATP)
7440-70-2 (CALCIUM)

L65 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN **1995:55622** BIOSIS
DN **PREV199598069922**
TI Extracellular ATP inhibits agonist-induced mobilization of internal calcium in human platelets.
AU **Soslau, Gerald**; McKenzie, Robert J.; Brodsky, Isadore; Devlin, Thomas M.
CS Hahnemann Univ., Dep. Biochem., Broad and Vine Sts., Philadelphia, PA, USA
SO Blood, (1994) Vol. 84, No. 10 SUPPL. 1, pp. 322A.
Meeting Info.: **Abstracts Submitted to the 36th Annual Meeting of the American Society of Hematology.** Nashville, Tennessee, USA. December 2-6, 1994.
CODEN: BLOOAW. ISSN: 0006-4971.
DT **Conference; (Meeting)**
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 31 Jan 1995
Last Updated on STN: 1 Feb 1995
CC **General biology - Symposia, transactions and proceedings 00520**
Cytology - Human 02508

Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Metabolism - Minerals 13010
Blood - Blood cell studies 15004
Endocrine - Neuroendocrinology 17020
Nervous system - Physiology and biochemistry 20504
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Endocrine System (Chemical Coordination and Homeostasis); Metabolism; Nervous System (Neural Coordination)
IT Chemicals & Biochemicals
ATP; CALCIUM; UTP; CTP; U-46619
IT Miscellaneous Descriptors
ATP ANALOGUES; CTP; **MEETING ABSTRACT**; **MEETING POSTER**; PURINERGIC RECEPTORS; U-46619; UTP
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 56-65-5Q (ATP)
42530-29-0Q (ATP)
94587-45-8Q (ATP)
111839-44-2Q (ATP)
7440-70-2 (CALCIUM)
63-39-8 (UTP)
65-47-4Q (CTP)
103335-28-0Q (CTP)
216768-11-5Q (CTP)
56985-40-1 (U-46619)
87805-51-4Q (ATP)

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SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<

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L84 ANSWER 1 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **2004-156422** [15] WPIX
DNN **N2004-125194** DNC **C2004-062099**
TI New modified **PAR** polypeptide, comprising non-functional endogenous **activating** peptide and interacting with an exogenous ligand for a wild-type **PAR receptor** useful for selecting compounds that modulate the activity of **PAR receptor.**
DC B04 D16 S03
IN BERTHELIER, C; BIGOGNE, C; MILANO, S; NORMANT, E
PA (PFIZ) PFIZER INC
CYC 105
PI WO 2004003202 A1 20040108 (200415)* EN 120p C12N015-12
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
FR 2841559 A1 20040102 (200415) C07K014-705
ADT WO 2004003202 A1 WO 2003-EP6822 20030627; FR 2841559 A1 FR 2002-8173 20020628
PRAI FR 2002-8173 20020628
IC ICM C07K014-705; C12N015-12
ICS C12N005-10; C12N015-63; C12Q001-02; G01N033-50; G01N033-566; G01N033-68
AB WO2004003202 A UPAB: 20040302
NOVELTY - A modified **PAR** polypeptide, comprising its endogenous **activating** peptide made non-functional and being capable of interacting with an exogenous ligand for a wild-type **PAR receptor**, where the exogenous ligand has an ED50 for the modified **PAR** polypeptide significantly higher than its ED50 for a wild type **PAR receptor**, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a polynucleotide encoding the polypeptide;
(2) an expression vector comprising the polynucleotide;
(3) a recombinant host cell comprising the polynucleotide;
(4) preparing a modified **PAR** polypeptide comprising obtaining a polynucleotide encoding the modified **PAR** polypeptide; inserting the polynucleotide into an expression vector that is functionally linked to a promoter; and producing the modified **PAR** polypeptide from the polynucleotide;
(5) screening for, selecting or identifying **PAR** activity modulator compounds comprising bringing a test compound into contact with a modified **PAR** polypeptide; and selecting the compounds that bind to the modified **PAR** polypeptide or determining the activity of the modified **PAR** polypeptide; and
(6) a kit for the in vitro screening, selection or identifying of **PAR** activity modulator compounds comprising the polypeptide, or recombinant host cell, and optionally, the reagents necessary to perform the **PAR** polypeptide activity measurement.

ACTIVITY - Antiinflammatory; Antiallergic; CNS-Gen.; Cardiovascular-Gen.; Neuroleptic. No biological data given.

MECHANISM OF ACTION - None given.

USE - The polypeptide is useful for selecting compounds that modulate the activity of at least one **PAR receptor.** The kit is useful for the in vitro screening, selection or identifying of **PAR** activity modulator compounds (all claimed). The compounds identified are useful for treating inflammation, allergies, diseases affecting the CNS, psychiatric or cardiovascular diseases.

Dwg.0/6
FS CPI EPI
FA AB
MC CPI: B04-E02D; B04-E08; B04-F0100E; B04-K0100E; B11-C08F; B11-C10; **B12-K04E**; B14-C03; B14-F01; B14-F02; B14-G02A; B14-J01; D05-C12; **D05-H09**; D05-H12B; D05-H12E; D05-H14; D05-H17B4
EPI: S03-E13D; S03-E14H
TECH UPTX: 20040302
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Polypeptide: The modified **PAR** polypeptide comprises an exogenous ligand having an ED50 for the polypeptide at least 5, 10 or 50 times higher than its ED50 for a wild-type **PAR receptor.** The region that extends from the first N-terminal residue of the **PAR** polypeptide up to a residue between the first N-terminal residue of the endogenous **activating** peptide and the last C-terminal residue of the amino-terminal extracellular domain is deleted. The **PAR receptor** is chosen from **PAR-1**, **PAR-2**, **PAR-3** and **PAR-4.** The polypeptide comprises a sequence of 355, 341 or 320 amino acids fully defined in the specification. The polynucleotide comprises a sequence of 1068, 1026, or 963 bp, fully defined in the specification. It comprises a sequence that differs from those cited above due to the degeneracy of the genetic code.
Preferred Cell: The host cell does not express any wild-type **PAR receptor.** The recombinant host cell also expresses a reporter gene for detecting or measuring the activity of the modified **PAR** polypeptide.
Preferred Method: The screening method comprises bringing a test compound into contact with the **PAR** polypeptide; and selecting the compounds that bind to the modified **PAR** polypeptide or determining the activity of the modified **PAR** polypeptide.
This method comprises:
(a) providing a recombinant host cell expressing the modified **PAR** polypeptide in an appropriate culture medium;
(b) adding a desired concentration of a test compound in the culture medium;
(c) adding a reference ligand in the culture medium;
(d) measuring the activity of the modified **PAR** polypeptide; and
(e) comparing the activity of the modified **PAR** polypeptide obtained with the its activity when the adding step is omitted.
The modified **PAR** polypeptide activity is measured through calcium release measurement. The **PAR** polypeptide activity measure is direct.
The method alternatively comprises:
(a) providing a recombinant host cell co-expressing a modified **PAR** polypeptide and a reporter gene;
(b) adding a desired concentration of a test compound in the culture medium;
(c) adding a reference ligand in the culture medium;
(d) measuring the reporter gene expression; and
(e) comparing the reporter gene expression obtained with the reporter gene expression when the adding step is omitted.
The recombinant host cell consists of a CHO (Chinese hamster ovary) cell line. The reporter gene is a beta-lactamase gene, which is placed under the control of a promoter comprising an NFAT domain sensitive to Ca2+ ions. The modified **PAR** polypeptide is a modified **PAR-2** polypeptide. The reference ligand is selected from Ser-Leu-Ile-Gly-Arg-Leu, Ser-Leu-Ile-Gly-Lys-Val, Ser-Leu-Ile-Gly-Arg, propionyl-tc, trans-cinnamoyl-Leu-Ile-Gly-Arg-Leu-O and Ser-Phe-Leu-Leu-Arg.

L84 ANSWER 2 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **2003-845191** [78] WPIX

DNC **C2003-237480**
TI Treatment of angiogenesis-associated diseases comprises administering composition comprising **Protease-Activated Receptor** (**PAR**) agonist, e.g. monoclonal antibody, capable of binding directly to the **PAR receptor.**
DC B04 D16
IN CHAN, B; MERCHAN, J; SUKHATME, V P
PA (BETH-N) BETH ISRAEL DEACONESS MEDICAL CENT
CYC 103
PI WO 2003079978 A2 20031002 (200378)* EN 77p A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2003079978 A2 WO 2003-US8121 20030314
PRAI US 2002-365165P 20020318
IC ICM A61K000-00
AB WO2003079978 A UPAB: 20031203
NOVELTY - Treating angiogenesis-associated diseases, comprising administering a pharmaceutical composition comprising a **Protease-Activated Receptor** (**PAR**) agonist, where the agonist is capable of binding directly to the **PAR receptor**, is new.
DETAILED DESCRIPTION - Treating (M1) angiogenesis-associated diseases, comprising:
(a) administering a pharmaceutical composition comprising a **Protease-Activated Receptor** (**PAR**) agonist, where the agonist is capable of binding directly to the **PAR receptor**;
(b) administering a compound which results in **activation** of a **protease-Activated Receptor** (**PAR**), where the treatment does not comprise administering either tissue plasminogen **activator** (tPA) polypeptide or a urokinase plasminogen **activator** (uPA), where the uPA is capable of binding to the human uPA **receptor** (uPA-R) in combination with captopril;
(c) administering a pharmaceutical composition comprising **thrombin** or **prothrombin** to a patient diagnosed with an angiogenesis associated disease;
(d) administering a pharmaceutical composition comprising a compound that modulates **PAR** biological activity, where the treatment does not comprise administering either tPA polypeptide or a uPA, where the uPA is capable of binding to the human uPA-R if the treatment also comprises administering captopril;
(e) administering a pharmaceutical composition comprising substantially pure urokinase (uPA) polypeptide, where the polypeptide is incapable of binding to the urokinase **receptor**, uPA-R;
(f) introducing a transgene encoding a uPA polypeptide, where the uPA polypeptide is incapable of binding to uPA-R, to a cell, the transgene is operably linked to expression control sequences, and the transgene being positioned for expression in the cell; or
(g) introducing a transgene encoding a **PAR** polypeptide, the transgene is operably linked to expression control sequences, and the transgene being positioned for expression in the cell.
INDEPENDENT CLAIMS are also included for:
(1) a pharmaceutical composition (I) comprising substantially pure **PAR**-agonist, where the agonist is capable of binding directly to the **PAR receptor**;
(2) a pharmaceutical composition (II) comprising a compound which results in **activation** of **PAR receptor**, where the composition does not comprise either tPA polypeptide or uPA, where the

uPA is capable of binding to the human uPA **receptor**;

(3) identifying (M2) candidate compounds that modulate **PAR** biological activity, comprising contacting the **PAR** to a candidate compound, and measuring binding of the compound to the **PAR receptor**; and

(4) identifying (M3) antiangiogenic molecules in serum plasma, comprising contacting the serum plasma with a tissue **protease** and an ACE inhibitor, depleting the plasma of angiostatin, chromatographically separating plasma fractions, and determining angiogenic potential of the fraction, where inhibition of angiogenesis identifies the fraction as antiangiogenic.

ACTIVITY - Cytostatic; Antirheumatic; Antipsoriatic; Cytostatic; Anti-HIV; Antidiabetic; Ophthalmological; Vulnerary. No biological data given.

MECHANISM OF ACTION - Inhibitor of angiogenesis; Gene Therapy. No biological data given.

USE - (M1) is useful for treating angiogenesis-associated diseases chosen from cancer, rheumatoid arthritis, psoriasis, pyogenic granuloma, HIV Kaposi's sarcoma, diabetic retinopathy, muscular degeneration, corneal graft neovascularization, and hypertrophic scarring. In (M1), the angiogenesis-associated disease is preferably cancer. (M1) further comprises administering antiproliferative agent simultaneously or within 14 days of each other in amounts sufficient to inhibit the growth of the neoplasm. A pharmaceutical composition (I) comprising substantially pure **PAR**-agonist (I) or a pharmaceutical composition (II) comprising a compound which results in **activation** of **PAR receptor** (II) is useful for the treatment of an angiogenesis associated disease. The angiogenesis associated disease is cancer. The cancer is breast cancer. (I) or (II) further comprises a second therapeutic agent. The second therapeutic agent is an antiproliferative agent (all claimed).

DESCRIPTION OF DRAWING(S) - The figure shows bar graph showing the effects of tissue **protease** overexpression on tumor cell growth.

Dwg.15/15

FS CPI

FA AB; GI; DCN

MC CPI: B04-B04D4; B04-E08; B04-G01; B04-G21; **B04-H19**; B04-L01; B05-B01E; B06-D01; B06-D03; B06-D04; B07-D03; B11-C10; **B12-K04E**; B14-C09B; B14-H01; B14-N03; B14-N17B; B14-N17C; B14-S03A; B14-S04; **D05-H09**; D05-H11A

TECH UPTX: 20031203

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred **Receptor**: In (M1), the **PAR** is chosen from **PAR-1**, **PAR-3**, and **PAR-4**.

Preferred Agonist: The **PAR**-agonist or **activator** of the **PAR receptor** is chosen from polypeptides such as (P1)-(P5).

Ser-Phe-Leu-Leu-Arg-Asn-Pro-Asn-Asp-Lys-Tyr-Glu-Pro-Phe (P1)
Ser-Phe-Leu-Leu-Arg-Asn (P2)
Ser-Ala-Leu-Leu-Arg-Asn (P3)
Gly-Tyr-Pro-Gly-Lys-Phe (P4)
Ser-Leu-Ile-Gly-Lys-Val (P5)

The **PAR**-agonist is a monoclonal antibody. The monoclonal antibody modulates **PAR-receptor** signaling. The monoclonal antibody further prevents **receptor** internalization.

Preferred Method: (M1) further comprises administering an anti-coagulant. (M1) further comprises administering an ACE inhibitor which is chosen from captopril, enalapril, lisinopril, benazepril, fosinopril, ramipril, quinapril, perindopril, trandolapril, and moexipril. The serum plasma is mammalian serum plasma. The tissue **protease** is chosen from urokinase, tissue plasminogen **activator**, and streptokinase. In (M1) the fraction having antiangiogenic activity is further purified to allow for identification. The uPA is mouse, rat, or human. Preferably, uPA

is human uPA. The human uPA further comprises amino acid substitutions within the OMEGA-loop. The OMEGA-loop comprises amino acid residue substitutions on the amino acid sequences chosen from Tyr24-Phe25-Ser26-Asn27-Ile28-His29-Trp30 in human, Tyr24-Phe25-Ser26-Arg27-Ile28-Arg29-Arg30 in mouse, and Tyr24-Phe25-Ser26-Ser27-Ile28-Arg29-Arg30 in rat. (M1) comprises administering an antiproliferative agent. The transgene is operably linked to tissue-specific expression control sequences. Preferred Composition: (I) or (II) comprises uPA, where the uPA is incapable of binding to the uPA-**receptor**, and a carrier.

ABEX UPTX: 20031203

ADMINISTRATION - (I) or (II) is administered by parenteral, intravenous, intraarterial, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, or oral routes. No dosage given.

L84 ANSWER 3 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **2003-679959** [64] WPIX
DNC **C2003-185832**
TI Predicting pathological conditions in heart failure using marker genes and proteins.
DC B04 D16
IN ASAKURA, M; FURUKAWA, H; ISOMURA, T; KITAKAZE, M; KOISHI, R; NAKAMARU, K; TAKASHIMA, S
PA (SANY) SANKYO CO LTD
CYC 30
PI WO 2003072824 A1 20030904 (200364)* JA 137p C12Q001-68
RW: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR
W: AU CA IL US
JP 2004000155 A 20040108 (200405) 75p C12N015-09
ADT WO 2003072824 A1 WO 2003-JP2228 20030227; JP 2004000155 A JP 2003-50597 20030227
PRAI JP 2002-112228 20020415; JP 2002-54388 20020228
IC ICM C12N015-09; C12Q001-68
ICS A61K031-7088; A61K038-00; A61K039-395; A61K048-00; A61P009-04; C12N015-12; C12Q001-02
AB WO2003072824 A UPAB: 20031006
NOVELTY - Predicting pathological conditions in heart failure using expression of one of 17:

(1) gene sequences encoding e.g. xenotropic retrovirus **receptor**, somatostatin **receptor** (isoform 1), G-protein coupled **receptor** (**GPCR**) 3, 15 or 35, endothelin type b **receptor**-like protein 2 galanin **receptor**, or formyl **receptor**, fully defined in the specification; or

(2) protein sequences encoded by the genes, fully defined in the specification, is new.

DETAILED DESCRIPTION - Predicting pathological conditions in heart failure using expression of one of 17:

(1) gene sequences encoding xenotropic retrovirus **receptor**, somatostatin **receptor** (isoform 1), G-protein coupled **receptor** (**GPCR**) 3, 15 or 35, endothelin type b **receptor**-like protein 2 galanin **receptor**, formyl **receptor**, coagulation factor II **receptor**-like 2 **proteinase-activated receptor** 3 or endothelial differentiation, sphingolipid **GPC**, fully defined in the specification; or

(2) protein sequences encoded by the genes, fully defined in the specification, is new.

INDEPENDENT CLAIMS are included for the following:

(1) medical compositions for treating heart failure containing the genes or proteins, antisense nucleic acids to the genes, or antibodies against the proteins; and

(2) a kit for carrying out the method.

ACTIVITY - Cardiant.
MECHANISM OF ACTION - Antisense therapy; Gene therapy; G-protein coupled **receptor** antagonist; Xenotropic retrovirus **receptor** antagonist; Somatostatin **receptor** antagonist; Formyl **receptor** antagonist. No biological data given.
USE - The proteins and genes are useful for diagnosis, treatment and prevention of heart failure.
Dwg.0/1

FS CPI
FA AB; DCN
MC CPI: B04-E03D; B04-E03F; B04-E06; B04-E12; B04-G01; B04-G04; B04-K01; B04-N02; B11-C08F; B12-K04A2; B14-F01B; B14-S03; **D05-H09**; D05-H11; D05-H12A; D05-H12D2
ABEX UPTX: 20031006
EXAMPLE - Using expression data from healthy heart tissue and that from a failed heart, G-protein coupled **receptor** (**GPCR**) gene data was extracted and marker genes that are expressed at different levels in healthy and diseases tissue were selected. The genes that showed an average difference value of more than 50 were those with nucleic acids sequences fully defined in the specification.

L84 ANSWER 4 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **2002-750452** [81] WPIX
DNN **N2002-591051** DNC **C2002-212633**
TI New isolated and purified **PAR-4** nucleic acid molecule and protein, useful for screening assays to detect compounds that bind to the protein or protein fragment, and for a small animal model of **thrombosis.**
DC B04 D16 S03
IN ADDO, M; ANDRADE-GORDON, P; DARROW, A; DERIAN, C
PA (ORTH) ORTHO-MCNEIL PHARM INC
CYC 100
PI WO 2002070564 A2 20020912 (200281)* EN 63p C07K014-705
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
EP 1363947 A2 20031126 (200380) EN C07K014-705
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002070564 A2 WO 2002-US5946 20020226; EP 1363947 A2 EP 2002-713702 20020226, WO 2002-US5946 20020226
FDT EP 1363947 A2 Based on WO 2002070564
PRAI US 2001-798279 20010302
IC ICM C07K014-705
ICS C07K016-28; C12N005-10; C12N015-12; G01N033-50
AB WO 200270564 A UPAB: 20021216
NOVELTY - An isolated and purified nucleic acid molecule (I) encoding guinea pig **Protease Activated Receptor**-4 (**PAR-4**) protein comprises:
(i) sequence having at least 75% identity to a polypeptide with a fully defined sequence of 388 amino acids (S1), given in the specification;
(ii) complement of (i);
(iii) at least 15 sequential bases of (i) or (ii); and
(iv) sequence hybridizing under stringent conditions to (i).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) isolated and purified nucleic acid molecule (II) encoding a **PAR-4** fusion protein comprising at least amino acids 219-243 of guinea pig **PAR-4**;

(2) expression vector (III) for expression of a guinea pig **PAR-4** protein in a recombinant host, where the vector comprises a nucleic acid molecule that hybridizes under stringent conditions to a fully defined sequence of 1228 bp, given in the specification;

(3) substantially pure protein (IV) comprising a sequence of at least 15 consecutive amino acids corresponding to amino acids 219-243 of S1;

(4) recombinant host cell (V) comprising (III);

(5) monospecific antibody (VI) immunologically reactive with guinea pig **PAR-4** protein;

(6) cellular membrane fraction (VII) obtained from (V);

(7) expressing (M1) guinea pig **PAR-4** protein in a recombinant host cell comprising introducing (III) into suitable host cells, and culturing the host cells under conditions which allow expression of the guinea pig **PAR-4** protein;

(8) **PAR activating** peptide (VIII);

(9) monospecific antibody immunologically reactive with (VII);

(10) method (M2) comprising admixing in an aqueous environment a guinea pig **PAR-4 activating** peptide (AP) with a cell or tissue, incubating the **PAR-4 activating** peptide and the cell or tissue for a predetermined amount of time, and measuring the interaction of the peptide with the cells;

(11) promoting (M3) human **platelet aggregation** comprising combining an **aggregating** amount of an **activating** peptide with human **platelets** where the peptide comprises Sequence A;

(12) determining (M4) whether a substance is capable of inhibiting guinea pig **PAR-4** activity comprising giving a test substance and an **activating** peptide to a guinea pig, where the peptide comprises Sequence A, and measuring the ability of the test substance to inhibit **PAR-4 activation** in the guinea pig as compared to a control guinea pig that did not receive the substance;

(13) determining (M5) whether a substance capable of interfering with the interaction between an **activating** peptide and a **PAR -4** protein comprising adding a test substance and an **activating** peptide to a cell membrane composition comprising a **PAR-4** protein where the peptide comprises Sequence A, measuring the amount of binding of the peptide to the cell membrane composition, and comparing the amount of binding of the peptide to the composition to an amount of binding of the peptide in control cells receiving no test substance;

(14) compound identified by using M4 and M5; and

(15) peptide consisting of at least 15 consecutive amino acids from S1.

USE - (I) or the protein or protein fragment encoded is useful in screening assays to detect compounds that bind to the protein or protein fragment (claimed). The guinea pig **PAR-4** protein is useful in a small animal model of **thrombosis. PAR activating** peptides are useful as ligands to **activate** human **PAR4.**

Dwg.0/4

FS CPI EPI

FA AB; DCN

MC CPI: B04-B04D5; B04-C01C; B04-C01G; B04-E01; B04-F01; B04-F0100E; B04-G04; B04-G21; B04-K0100E; B04-N02A0E; B04-P01A; B11-C08; B11-C10; **B12-K04A**; **B12-K04E**; B14-L01; B14-L06; D05-C12; **D05-H09**; D05-H11A; D05-H12A; D05-H12D1; D05-H12E; D05-H14B2; D05-H17A4; D05-H18

EPI: S03-E14H4

TECH UPTX: 20021216

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Nucleic Acid: (I) is RNA or

DNA. (I) further comprises any of the fully defined sequences of 2428 or 1228 bp, given in the specification.
Preferred Vector: The expression vector comprises nucleic acid corresponding to any of the fully defined sequences of 2428 or 1228 bp, given in the specification. The expression vector encodes the guinea pig **PAR-4** protein of S1. The vector further comprises a genomic DNA encoding guinea pig **PAR-4** protein.
Preferred Protein: (IV) has a molecular weight of 41-55 kD. The protein further comprises S1.
(VIII) comprises the sequence (SEQUENCE A) SFPGQ(X)n where
X = any amino acid or amino acid derivative
and where
n = 0-30
Preferred Antibody: The antibody blocks activity of the guinea pig **PAR-4** protein, and is preferably a monoclonal antibody.
Preferred Method: The cell in M2 is in vitro or in vivo. The interaction of the peptide with the cell is detected by measuring the **activation** of a **PAR.** The cell membrane composition in M5 is a cell membrane fraction. The cell membrane composition is **part** of an intact cell or isolated tissue or organ sample. The cells are **platelets** and the measuring of the amount of binding comprises measuring the amount of **platelet aggregation**, calcium mobilization, ADP degranulation or cell shape change. M5 is preferably performed in a guinea pig. The **activating** peptide is labeled and the measuring of the amount of binding step comprises measuring the amount of label bound to the cell membrane composition.
Preparation: (I) was isolated using standard recombinant techniques.

ABEX UPTX: 20021216

SPECIFIC SEQUENCES - (I) has any of the specifically claimed fully defined sequences of 2428 or 1228 bp, given in the specification.

EXAMPLE - A probe corresponding to nucleotides 329-786 of human **PAR-4** was labeled by random priming and used to screen 3 x 106 phage plaques of a gamma FIX II guinea pig genomic library under low stringency hybridization using Rapid-hyb Buffer for a minimum of 15 hours at 55degreesC. Washes were carried put with two 20 minutes washes of 2 x standard citrate saline/ 0.1% SDS and two 20 minute washes of 0.2 x SSC/ 0.1 % SDS at 55degreesC. 2 positives were isolated and following plaque purification, the entire genomic DNA inserts of both clones were independently subcloned into Not I site of the plasmid vector pKS II. A cross-hybridizing 1.3Kb Pst 1 restriction fragment, common to both genomic clones, was subcloned and subjected to sequence analysis. This fragment was found to contain all the coding sequence in exon2 from the presumptive **activation** sequence to the stop codon. sequence surrounding this Pst 1 fragment was obtained from the original guinea pig **PAR-4** genomic clones to partial sequence analysis and a compliation of this region is represented as a fully defined 2428 base pair sequence.

L84 ANSWER 5 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-698632 [75] WPIX
DNN N2002-550903 DNC C2002-197842
TI Preventing **platelet aggregation** or treating cardiovascular disorders related to **thrombotic** events comprises administering a histone compound .
DC B04 D16 P32
IN CLASS, R; **SOSLAU, G**; ZEPPEZAUER, M
PA (PHIL-N) PHILADELPHIA HEALTH & EDUCATION CORP; (SYMB-N) SYMBIOTEC GMBH
CYC 101
PI WO 2002067907 A1 20020906 (200275)* EN 13p A61K009-70
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR

KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

EP 1370248 A1 20031217 (200402) EN A61K009-70

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR

ADT WO 2002067907 A1 WO 2002-US5157 20020222; EP 1370248 A1 EP 2002-706353 20020222, WO 2002-US5157 20020222

FDT EP 1370248 A1 Based on WO 2002067907

PRAI US 2001-270759P 20010222

IC ICM A61K009-70

ICS A61F002-00; A61K009-22; A61K009-50; A61K031-00; A61K051-08; B01J013-08; C12N011-02

AB WO 200267907 A UPAB: 20021120

NOVELTY - Preventing **platelet aggregation** or treating cardiovascular disorders related to **thrombotic** events comprises administering a histone compound and a vehicle to the patient.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) composition for preventing **platelet aggregation** comprising a histone compound and a vehicle; or

(2) implantable device comprising a device that is coated with a histone compound that is to be inserted into the body of a patient.

ACTIVITY - Cardiant; Anticoagulant.

Test details are described but no results given.

MECHANISM OF ACTION - **Thrombin** inhibition by blocking **gamma -thrombin**-induced **platelet aggregation.**

USE - The method is useful for preventing **platelet aggregation** or treating cardiovascular disorders related to **thrombotic** events (claimed). Histone compounds can also be used to coat implantable devices such as stents or valves, or to coat devices inserted into the body of a patient, such as catheters.

Dwg.0/0

FS CPI GMPI

FA AB; DCN

MC CPI: B04-C01; B04-H0100E; B04-N0200E; B11-C04A; B14-F01; B14-F04; B14-L06; D05-C12; D05-H17A6

TECH UPTX: 20021120

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compound: The histone compound, which is human, comprises H1, H2A, H2B, H3 or H4. H1 histone is a histone subtype H1.0, H1.1, H1.2, H1.3, H1.4 or H1.5 and is recombinantly produced. It is administered prophylactically.

ABEX UPTX: 20021120

SPECIFIC COMPOUNDS - The histone compound, which is human, comprises H1, H2A, H2B, H3 or H4. H1 histone is a histone subtype H1.0, H1.1, H1.2, H1.3, H1.4 or H1.5 and is recombinantly produced. H1 histone is a histone subtype H1.0, H1.1, H1.2, H1.3, H1.4 or H1.5.

ADMINISTRATION - Compositions in solution can be injected intravenously, intramuscularly, subcutaneously, intraperitoneally or instilled directly into the eye or mucosal areas. No dosage given.

L84 ANSWER 6 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN **2002-682036** [73] WPIX

DNC **C2002-192387**

TI Screening for **antithrombin** and **antiplatelet** compounds for treating cardiovascular disease comprises testing for inhibition of **GP Ib**, **PAR-1** or **PAR-4 receptor** binding.

DC B04 D16

IN **SOSLAU, G**

PA (SOSL-I) SOSLAU G

CYC 1
PI US 2002103107 A1 20020801 (200273)* 5p C12Q001-56 <--
ADT US 2002103107 A1 Provisional US 2000-257067P 20001221, US 2001-29611 20011221
PRAI US 2000-257067P 20001221; US 2001-29611 20011221
IC ICM **C12Q001-56**
ICS A61K031-00
AB US2002103107 A UPAB: 20021113
NOVELTY - Screening (M1) for compounds with **antithrombotic/antiplatelet** activity comprising incubating test compounds with **platelets** in vitro and testing for ability to inhibit **platelet aggregation** through inhibition of:
(a) **GP Ib**, **PAR-1** or **PAR-4 receptor** binding; or
(b) **alpha -thrombin**, **beta -thrombin** or **gamma-thrombin pathways**,
is new.
USE - (M1) is useful for screening for compounds with **antithrombotic/antiplatelet** activity (claimed) which may be useful in treating cardiovascular disease.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-F04; **B04-H19**; B04-K01R; B04-N06; B11-C07B; B11-C08E1; **B12-K04E**; B14-F01; **D05-H09**
ABEX UPTX: 20021113
EXAMPLE - No suitable example is given.

L84 ANSWER 7 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **2002-315494** [35] WPIX
DNN **N2002-246915** DNC **C2002-091848**
TI Identifying agent inhibiting **thrombin**-induced **platelet activation**, by administering test agent and proteolytically inactive **thrombin** to **GP** V null non-human transgenic animal and monitoring **platelet aggregation.**
DC B04 D16 P14 S03
IN PHILLIPS, D; RAMAKRISHNAN, V
PA (CORT-N) COR THERAPEUTICS INC
CYC 97
PI WO 2002017711 A2 20020307 (200235)* EN 64p A01K067-027
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001086900 A 20020313 (200249) A01K067-027
ADT WO 2002017711 A2 WO 2001-US26936 20010831; AU 2001086900 A AU 2001-86900 20010831
FDT AU 2001086900 A Based on WO 2002017711
PRAI US 2000-230566P 20000831; US 2000-229047P 20000831
IC ICM A01K067-027
ICS A61P007-00; G01N033-86
AB WO 200217711 A UPAB: 20020603
NOVELTY - Identifying (M1) agent that inhibits **thrombin** (T)-induced activity (A) (e.g., **platelet** (P) **activation**), where (A) is modulated (inhibited) by **GP** V, by administering test agent and (proteolytically inactive) (T) to a **GP** V null non-human transgenic animal (I), and monitoring **aggregation** of (P) of (I) to identify inhibition. (M1) optionally involves using (P) isolated from (I) to identify modulator of (T), is new.
DETAILED DESCRIPTION - Identifying (M1) agent that inhibits **thrombin** (T)-induced activity (A) (e.g., **platelet** (P)

activation), where (A) is modulated (inhibited) by **GP** V, by administering test agent and (proteolytically inactive) (T) to a **GP** V null non-human transgenic animal (I), and monitoring **aggregation** of (P) of (I) to identify inhibition. (M1) optionally involves using (P) isolated from (I) to identify modulator of (T). (M1) involves administering test agent and (proteolytically inactive) (T) to (I), and monitoring **aggregation** of (P) of (I) to identify inhibition. Optionally (M1) involves administering a test agent and (T) using (P) isolated from (I) and monitoring **aggregation** of (P) for modulation of the activity. Screening for anti-**thrombotic** agents alternatively involves contacting (P) that does not display **GP** V on its surface within agent, contacting (P) with the **GP Ib**-IX signaling **activator**, and determining **GP Ib**-IX mediated signal transduction level, where a reduced level is indicative of an anti-**thrombotic** agent. Identifying (M1) an agents that inhibits **thrombin**-induced **platelet activation**, where the **activation** is modulated by **GP** V, involves administering a test agent and proteolytically inactive **thrombin** to a (I), and monitoring **aggregation** of **platelets** of the animal to identify inhibition. Identifying (M2) an agent that inhibits **thrombin** -induced activity, where the activity is inhibited by **GP** V involves administering a test agent and **thrombin** to a **platelet** isolated from (I) and monitoring **aggregation** of **platelets** to identify modulation of activity. Identifying an agent that modulates **thrombin** activity, where the activity is inhibited by **GP** V involves administering a test agent and **thrombin** to **platelet** isolated from (I) and monitoring **aggregation** of **platelets** to identify modulation of activity.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising a **platelet** that does not display **GP** V on its surface; and a **GP Ib**-IX signaling **activator**;

(2) determining (M2) predisposition to **thrombosis** in a subject by determining level of **GP** Vf1 in a blood sample from the subject, where **GP** Vf1 presence in the sample indicates predisposition to **thrombosis.** The method optionally involves determining level of **GP** V on **platelets** derived from the subject, where decrease in the level of **GP** V on **platelets** is indicative of the predisposition **thrombosis** ;

(3) inhibiting (M3) **thrombosis** in a subject involves administering to a subject, an inhibitor of **GP Ib**-IX signal transduction, with the proviso that the agent is not heparin;

(4) screening (M4) for **antithrombotic** agents, involves contacting a **platelet** that does not display **GP** V on its surface with an agent, contacting the **platelet** with a **GP Ib**-IX signaling **activator**, and determining **GP Ib**-IX mediated signal transduction level, where a reduced level is indicative of an **antithrombotic** agent;

(5) preventing (M5) **platelet activation** in a subject, involves administering to the subject an agent that prevents interaction of **thrombin** exosite II with **GP Ib** -IX, with the proviso that the agent is not heparin;

(6) an agent (III) identified by (M1), where proteolytically inactive (T) is administered to (I); and

(7) a pharmaceutical composition (IV) comprising (III) to ameliorate a condition characterized by **platelet activation.**

ACTIVITY - Anticoagulant. No supporting data is given.

MECHANISM OF ACTION - **Platelet activation** inhibitor; **GP Ib**-IX signal transduction inhibitor; interaction of (T) exosite II with **GP Ib**-IX inhibitor.

USE - For identifying agents that inhibit (T)-induced activity e.g., (T)-induced (P) **activation**, and for screening anti-**thrombotic** agents. (M3) is useful for inhibiting **thrombosis** in a subject. (M5) is useful for preventing (P) **activation** in a subject (all claimed).
Dwg.0/14

FS CPI EPI GMPI
FA AB; DCN
MC CPI: B04-B04D5; B04-F04; **B04-H19**; B04-P0100E; B11-C08D; **B12-K04E**; B14-F04; D05-H08; **D05-H09**; D05-H11
EPI: S03-E14H1

TECH UPTX: 20020603
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: (T) used in (M1) may be proteolytically inactive, or may be an active (T). The proteolytically inactive (T) is phenylalaninylprolylargininylchlormethylketone (PPACK)-inactivated (T), S205A (T), or di-isopropylphospho (DIP)-(T). The test agent administered to (I) along with proteolytically inactive (T) binds **Ib**-IX, and is an antibody that specifically binds to **GP Ib**-IX or is an agent that binds exosite II of (T).
The test agent administered along with active (T), is an antibody that binds specifically to **GP Ib**-IX, peptide or small molecule. The **GP Ib**-IX **activator** is inactive (T), e.g., proteolytically inactive (T). The **GP Ib**-IX-mediated signal transduction level is determined by measuring (P) **aggregation.** In (M2), determining level of **GP** Vf1 is performed using an antibody specific for **GP** Vf1. Determining level of **GP** V on (P), is performed by fluorescence **activated** cell sorting (FACS) or by Western blot. In (M3), the inhibitor binds to exosite II of (T).
Preferred Composition: (II) contains a **GP Ib**-IX signaling **activator** which is a proteolytically inactive (T).
(II) further comprises an agent that modulates an activity of (P) induced by (T). The (T) used in the method may be a proteolytically inactive (T) as described above.

ABEX UPTX: 20020603
WIDER DISCLOSURE - The following are also disclosed as new:
(1) non-human transgenic animal (V), preferably mammals that contain or comprise a modified **GP** V gene;
(2) cells isolated from (V);
(3) preparing (V);
(4) comparing a characteristic between two mammals of same species, or strain, where one mammal has, for e.g., a wild-type **GP** V gene and the other mammal has a modified **GP** V gene; and
(5) comparing cells isolated from (V).

ADMINISTRATION - The agents are administered by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal or buccal route. Dosages range from 0.1-100 (preferably 0.1-1) microg/kg body weight.
EXAMPLE - To evaluate the specific role of **glycoprotein** V (**GP** V) in both **platelet** function and the **GP Ib**-IX-V complex expression, a mouse strain that lacked the **GP** V gene was generated using homologous recombination techniques. Analysis of whole blood from **GP** V-deficient animals showed the **platelets** were normal in both number and size. **Platelet** counts in whole blood were within the normal range. There was a statistically significant difference in **platelet** recovery from whole blood from wild-type ánimals and -/- animals. +/- animals showed intermediate recovery numbers, which were not statistically different. **Platelets** were isolated from the -/- animals to confirm that gene deletion resulted in absence of **GP** V protein expression and analyzed for **GP** V expression using **GP** V antibodies. No **GP** V protein was detectable either on the intact **platelet** surface using fluorescence **activated** cell sorting (FACS)

analysis or in total **platelet** lysates as determined by Western blotting. 2 assays were used to determine whether the **GP Ib** expressed on **GP** V -/- **platelets** was functional. One assay measured the adhesion of **platelets** to immobilized von Willebrand factor (vWF) that was **activated** by botrocetin to bind **GP Ib.** The **GP** V -/- **platelets** bound to immobilized, botrocetin-**activated** human vWf in a manner indistinguishable from wt **platelets.** Under these conditions, the binding of vWf to **platelets** was mediated entirely by **GP Ib**, since purified human glycocalicin (a soluble, extracellular fragment of **GP** Ibalpha that contains the vWf binding domain), inhibited botrocetin-induced binding of **platelets** to vWf in a concentration-dependent manner. Also the soluble, **activated** vWf bound identically to **platelets** from all 3 genotypes. Again, botrocetin-induced vWf binding could be completely inhibited by purified from glycocalicin. Furthermore, stimulation of alphaIIbbeta3 on **platelets** by ADP and epinephrine did not induce soluble vWf binding. Thus, **GP Ib**-IX expressed in the **GP** V -/- **platelets** was functional. The effect of **GPV** gene deletion on **thrombin**-induced **platelet** function was determined and results showed that **GP** V was a negative regulator of **platelet** function. Since **platelets** lacking **GP** V exhibited an increased **aggregation** response to **thrombin** compared to wt **platelets.** To determine the consequences of enhanced **platelet** function in **GP** V -/- mice, bleeding time measurements were performed using a tail cut model. **GP** V -/- mice had a statistically shorter bleeding time than wt littermate control mice. 70% of the -/- mice had bleeding times less than 120 sec, compared to 50% of the wt and +/- mice. Conversely, 21.6% of the wt mice had bleeding times greater than 500 sec, compared to 9.5% in the +/- mice and 8.5% in the -/- mice. Thus the increased aggregability of the **platelets** from **GP** V -/- mice observed in in vitro assays translates into a shorter bleeding time in vivo. To evaluate the physiological significance of the ligand binding function of **thrombin**, the effect of a systemic infusion of DIP-**thrombin** into mice was examined. Infusion of a **platelet** agonist induces a decrease in **platelet** counts due to (ongoing) **thrombosis.** There was significant **platelet** loss following the infusion of 10 nM **thrombin** in both **GP** V null and wt mice. Injection of 1 nM **thrombin** had a marginal effect on **platelet** counts in either **GP** V null mice or wt mice. In contrast, **GP** V null mice showed a significant **platelet** loss was minimal. As additional controls mutant CHO-expressed **thrombins** was used in which the exosite II has been mutated (R89/R93/E94 and R98A). These exosite II mutants were inactivated, and then injected into either **GP** V null or wt mice. There was no major loss in **platelets.** In contrasts, 460 nM CHO-expressed inactivated **thrombins** caused a significant **platelet** loss in **GP** V null mice, with little effect in wt mice. These results showed that binding of inactive forms of **thrombin** to **GP** V-deficient **platelets** can occur in vivo, and that the binding results in **platelet activation** and **thrombosis.** The data further substantiate the binding site for **GP** Ibalpha being via exosite II of **thrombin.** These results support a novel role for **GP** Ibalpha in **thrombin**-induced signaling in **platelets** which consequently supports **aggregation** and **thrombosis** . From further experiments carried out, a model for **thrombin** -induced **platelet activation** was established that involved not only the established **pathway** mediated by the **protease activated receptors** (**PARs**), but also a novel **pathway** in which the presence of **GP** V

in the **GP Ib**-IX-V complex inhibits the ability of **thrombin** to function as a **receptor** ligand. Following the loss of **GP** V upon cleavage by **thrombin**, **thrombin** binding to **GP** Ibalpha results in **activation** of alphaIIbbeta3 and consequently in **aggregation.** Thus, the **GP** Ibalpha-bound **thrombin** need not be catalytically functional for this response to occur. The data show not only a novel functional role for **thrombin**, but also a novel mechanism by which this **pathway** can mediate **thrombosis** independent of proteolytic activity.

L84 ANSWER 8 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **2002-188255** [24] WPIX
DNN **N2002-142767** DNC **C2002-058072**
TI New peptides modulating **protease-activated receptors**, useful for modulating **platelet activation** including clotting, particularly for treating e.g. myocardial infarction, stroke, pulmonary embolism or hemorrhage.
DC B04 D16 S03
IN COUGHLIN, S R; FARUQI, T R
PA (REGC) UNIV CALIFORNIA
CYC 21
PI WO 2001094411 A1 20011213 (200224)* EN 98p C07K014-705
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP US
ADT WO 2001094411 A1 WO 2000-US28958 20001019
PRAI US 2000-587718 20000605
IC ICM C07K014-705
ICS A61K038-08; A61P007-02; C07K007-06; G01N033-68
AB WO 200194411 A UPAB: 20020416
NOVELTY - Isolated peptides comprising peptides that **activate protease-activated receptors** (**PAR**) **1** or **PAR4**, are new.
DETAILED DESCRIPTION - The **PAR1** modulating peptide comprises GYPAKF, GYP(Cha)KF, GYPLKF, GYPIKF, S(F)(Cha)(Cha)(homoR)K or S(F)(Cha)(Cha)RK. The **PAR4** modulating peptide comprises GYPGRF, GYPG(homoR)F, GYPG(Orn)F, GYPGKY, GYPGKW, GYPGKK, SYPAKF, SYAGKF, SYPGRF or SYPG(homoR)F.
(Cha) = cyclohexylalanine;
(F) = parafluoro-phenylalanine;
(homoR) = homoarginine; and
(Orn) = ornithine.
INDEPENDENT CLAIMS are also included for the following:
(1) an expression vector comprising a polynucleotide encoding any of the isolated peptides;
(2) a host cell comprising the expression vector;
(3) pharmaceutical agents comprising: (a) the isolated peptides and a pharmaceutical excipient; (b) an isolated peptide selected from AYPGKF, SYPGKF or TYPGKF, and a pharmaceutical excipient; or (c) an isolated peptide selected from GFPGKF or G(F)PGKF, and a pharmaceutical excipient;
(4) methods for modulating **PAR4** activity or **PAR1** activity in an individual by administering the pharmaceutical agent to the individual;
(5) methods for modulating **platelet activation** in an individual by administering the agent to the individual;
(6) methods for modulating both **PAR1** and **PAR4** activity in an individual by administering the agent of (3c) to the individual;
(7) methods for identifying an agent that modulates **PAR4** or **PAR1** activity comprising: (a) contacting a host cell comprising **PAR4** or **PAR1** function with the agent to be tested, and the **PAR4** or **PAR1 activating** peptide; and (b) analyzing at least one characteristic that is associated with **PAR4**

or **PAR1** function in the host cell, where an agent is identified by its ability to modulate at least one such characteristic as compared to contacting the host cell with the **PAR4** or **PAR1** **activating** peptide without the agent;

(8) a method for identifying an agent that modulates both **PAR1** and **PAR4** activity comprising: (a) contacting a host cell comprising **PAR1** function with the agent to be tested and the **PAR1** and analyzing at least one characteristic that is associated with **PAR1** function in the host cell, where an agent is identified by its ability to modulate at least one such characteristic as compared to contacting the suitable host cell with the **PAR1** **activating** peptide without the agent; (b) contacting a host cell comprising **PAR4** function with the agent to be tested and the **PAR4 activating** peptide and analyzing at least one characteristic that is associated with **PAR4** function in the host cell, where an agent is identified by its ability to modulate at least one such characteristic as compared to contacting the suitable host cell with the **PAR4 activating** peptide without the agent; and (c) selecting an agent that modulates at least one characteristic associated with **PAR1** function and at least one characteristic associated with **PAR4** function, where the steps (a) and (b) are performed in any order or simultaneously;

(9) kits comprising any of the isolated peptides cited above; and

(10) a method for identifying an agent that antagonizes **PAR1** or **PAR 4** activity comprising: (a) contacting a host cell comprising **PAR1** or **PAR4** function with the agent to be tested and the **PAR1**; and (b) analyzing at least one characteristic that is associated with **PAR1** or **PAR4** function in the host cell, where an agent is identified by its ability to modulate at least one such characteristic as compared to contacting the suitable host cell with the **PAR1** or **PAR4** **activating** peptide without the agent.

ACTIVITY - Cerebroprotective; cardiant; antiarteriosclerotic; hemostatic; vulnerary.

No supporting data provided.

MECHANISM OF ACTION - **PAR** (**protease-activated receptors**) modulator.

The relative potencies of the peptides GYPGKF (native), SYPGKF and AYPGKF in phosphoinositide hydrolysis and cytoplasmic assays in KOLF-**PAR4** cells were compared. GYPGKF appeared to be a partial agonist for **PAR-4** triggered phosphoinositide hydrolysis; even at 500 micro m it elicited only approximately 50% of the maximal response to **thrombin.** SYPGKF and AYPGKF were full agonists for **PAR4 activation** and showed EC50's of 20 and 50 micro M respectively. AYPGKF stimulated calcium mobilization in KOLF-**PAR4** cells with an EC50 of 25 micro M, while more than 200 micro M of GYPGKF was required to elicit a similar response, showing that AYPGKF was more potent than GYPGKF. These data suggest that AYPGKF is instrinsically more active than GYPGKF at **PAR-4.**

USE - The peptides are useful for modulating **PAR1** or **PAR4.** In particular, the peptides are useful as therapeutic and/or prophylactic vaccines for modulating **platelet activation** including clotting. The peptides are useful for inhibiting inappropriate clotting in an individual, particularly for treating disorders such as myocardial infarction, stroke, pulmonary embolism, deep vein **thrombosis**, peripheral arterial occlusion or other blood system **thromboses.** The peptides are also useful for **activating** blood clotting in an individual to treat disorders involving insufficient clotting, e.g. hemorrhage. The peptides may also be used as an agent to screen pharmaceutical candidates (both in vitro and in vivo) or in drug design. In the method of (8), the host cell of step (a) lacks native **PAR1** function and comprises a recombinant polynucleotide encoding **PAR1** or its functional fragment, where **PAR1** function is

restored in the host cell. The host cell of step (b) has native **PAR4** function, where the host cell of step (b) lacks native **PAR4** function and comprises a recombinant polynucleotide encoding **PAR4** or its functional fragment, and where **PAR4** function is restored in the host cell. The method also involves identifying antagonists or agents that antagonize **PAR4** or **PAR1** activity by analyzing at least one characteristic associated with the inhibition of **PAR4** or **PAR1 activation** in the host cell. An agent is identified by its ability to modify at least one such characteristic as compared to contacting the host cell with the **PAR4** or **PAR1 activating** peptide without the agent.

DESCRIPTION OF DRAWING(S) - Figure showing calcium mobilization in human **platelets** following **PAR4** desensitization. Washed human **platelets** were loaded with FURA-2/AM and agonist triggered increases in cytosolic calcium was measured fluorometrically.

Dwg.0/8

FS CPI EPI
FA AB; DCN
MC CPI: B04-C01B; B04-E08; B04-F0100E; B11-C08E; **B12-K04E**; B14-D07C; B14-F01B; B14-F04; B14-F08; B14-K01; B14-N16; **D05-H09**; D05-H12D6; D05-H12E; D05-H14
EPI: S03-E14H
TECH UPTX: 20020416

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation:The peptides can be produced by recombinant methods or by chemical synthesis. Preferred Peptide: The peptide may be AYPGKF. The host cell has native **PAR4** or **PAR1** function. The host cell may also lack native **PAR4** or **PAR1** function, and comprises a recombinant polynucleotide encoding **PAR4** or **PAR1** or their functional fragment, where **PAR4** or **PAR1** function is restored in the host cell. In particular, the host cell is a **platelet** cell. The characteristic that is associated with **PAR4** or **PAR1** function is phosphoinositide hydrolysis, intracellular calcium mobilization, **platelet** shape change, **platelet** ATP (adenosine triphosphate) secretion or **platelet aggregation.**

ABEX UPTX: 20020416

ADMINISTRATION - Administration is by injection (e.g. intraperitoneally, intravenously, subcutaneously or intramuscularly). The amount of the agent is 0.001-100 mg/kg, preferably 0.01-10 mg/kg body weight of the individual (claimed) per week.

EXAMPLE - No relevant example given.

L84 ANSWER 9 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **2001-656678** [75] WPIX
DNC **C2001-193094**
TI Peptides comprising an amino acid sequence are capable of stimulating **protease-activated receptor** 4 which are useful in diagnosis and therapy e.g. inhibiting tumor cell proliferation and stimulating **platelet aggregation.**
DC B04 D16
IN BAINDUR, N; WEST, R R
PA (ZYMO) ZYMOGENETICS INC
CYC 94
PI WO 2001058930 A1 20010816 (200175)* EN 84p C07K007-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001033333 A 20010820 (200175) C07K007-06
EP 1254160 A1 20021106 (200281) EN C07K007-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2001058930 A1 WO 2001-US3807 20010206; AU 2001033333 A AU 2001-33333 20010206; EP 1254160 A1 EP 2001-905455 20010206, WO 2001-US3807 20010206
FDT AU 2001033333 A Based on WO 2001058930; EP 1254160 A1 Based on WO 2001058930
PRAI US 2000-500646 20000209
IC ICM C07K007-06
ICS A61K038-08; C07K014-705
AB WO 200158930 A UPAB: 20011220
NOVELTY - A peptide (I) comprising an amino acid sequence is new.
DETAILED DESCRIPTION - A peptide (I) comprises an amino acid sequence selected from
(a) Gly-Tyr-Pro-Gly-Gln-Val-Cys-NH2;
(b) Gly-Tyr-Pro-Gly-Gln-Val-Cys-Ala-NH2; and
(c) Gly-Xaa1-Pro-Gly-Lys-Xaa2-Xaa3-NH2,
Xaa1 = Tyr, Tyr(Me), Bip or 2-Nal;
Xaa2 = Phe, hPhe, Phe(4-F), Phe(4-Me), Thi, 1-Nal, 2-Nal or Bip; and
Xaa3 = Cys or Pen.
INDEPENDENT CLAIMS are also included for:
(1) a composition comprising a carrier and a peptide (I);
(2) a method of stimulating **platelet aggregation** by administering the composition to **platelets**; and
(3) a method of inhibiting tumor cell proliferation by administering the composition to tumor cells.
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - **Protease-activated receptor** 4 stimulator.
USE - (I) are capable of stimulating **protease-activated receptor** 4 which are useful in diagnosis and therapy e.g. inhibiting tumor cell proliferation and stimulating **platelet aggregation.**
ADVANTAGE - (I) mimic the N-terminus of the **activated** form of **protease-activated receptor** 4.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-C01B; B14-F08; B14-H01B; B14-L01; **D05-H09**
ABEX UPTX: 20011220
SPECIFIC POLYPEPTIDES - The following peptides are specifically claimed: Gly-Tyr-Pro-Gly-Lys-hPhe-Cys-NH2, Gly-Tyr(Me)-Pro-Gly-Lys-Phe-Cys-NH2, Gly-Tyr-Pro-Gly-Lys-Phe(4-F)-Cys-NH2, Gly-Tyr-Pro-Gly-Lys-Phe(4-Me)-Cys-NH2, Gly-Bip-Pro-Gly-Lys-Phe-Cys-NH2, Gly-2Nal-Pro-Gly-Lys-Phe-Cys-NH2, Gly-Tyr-Pro-Gly-Lys-Phe-Pen-NH2, and Gly-2Nal-Pro-Gly-Lys-Phe-Pen-NH2.

ADMINISTRATION - The composition is administered to a mammalian subject (claimed). Administration may be e.g. intravenous, intraarterial, intraperitoneal, intramuscular or oral. Dosage is 1 pg/kg to 10 mg/kg.

EXAMPLE - No preparative examples are given.

L84 ANSWER 10 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **2001-226546** [23] WPIX
DNC **C2001-067598**
TI Inhibiting **thrombin activation** in human cell expressing **protease activated receptor** 1 (**PAR1**), comprises contacting mixtures of **thrombin** and human cell expressing **PAR1**, with a peptide that inhibits

platelet activation.

DC B04
IN HASAN, A A K; SCHMAIER, A H
PA (THRO-N) THROMGEN INC; (UNMI) UNIV MICHIGAN
CYC 95
PI WO 2001012656 A1 20010222 (200123)* EN 49p C07K007-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000078822 A 20010313 (200134) C07K007-06
EP 1212352 A1 20020612 (200239) EN C07K007-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2003507389 W 20030225 (200317) 58p C07K007-18
US 6544750 B1 20030408 (200327) G01N033-53
AU 764707 B 20030828 (200361) C07K007-06
ADT WO 2001012656 A1 WO 2000-US40669 20000817; AU 2000078822 A AU 2000-78822 20000817; EP 1212352 A1 EP 2000-968987 20000817, WO 2000-US40669 20000817; JP 2003507389 W WO 2000-US40669 20000817, JP 2001-517554 20000817; US 6544750 B1 US 1999-375808 19990817; AU 764707 B AU 2000-78822 20000817
FDT AU 2000078822 A Based on WO 2001012656; EP 1212352 A1 Based on WO 2001012656; JP 2003507389 W Based on WO 2001012656; AU 764707 B Previous Publ. AU 2000078822, Based on WO 2001012656
PRAI US 1999-375808 19990817
IC ICM C07K007-06; C07K007-18; G01N033-53
ICS A61K038-00; A61P007-02; C07K007-08
AB WO 200112656 A UPAB: 20010425
NOVELTY - Inhibiting **thrombin activation** in a human cell expressing **protease activated receptor** 1 (**PAR1**), comprises providing a mixture comprising **thrombin** at a concentration effective to induce stimulus-response coupling within the cell, and a human cell expressing **PAR1**, and contacting the mixture with a compound (I) and (II) comprising at least one segment with an amino acid sequence (S1).

DETAILED DESCRIPTION - S1 is of formula Arg-Gly-Lys-Z4-Cys (I) or Arg-Gly-Asp-Z4-Cys (II), where Z4 is any naturally occurring amino acid, excluding cysteine. (I) comprises at most 10 amino acids in sequence.

INDEPENDENT CLAIMS are also included for the following:

(1) a method of binding a compound to biotinylated-peptide NATLDPRSFLLR (biotin-NAT12), providing a compound comprises (I) or (II), and incubating biotinNAT12 with (I) or (II); and

(2) a compound (I) comprising S1.

ACTIVITY - Anticoagulant.

MECHANISM OF ACTION - Inhibitor of **platelet aggregation**; inhibitor of **thrombin activation**; inhibitor of **thrombin** induced calcium mobilization in fibroblasts (claimed).

Fresh whole blood was collected and mixed with 0.013 M sodium citrate and **platelet**-rich plasma was prepared. **Platelet**-rich plasma with a normalized **platelet** count between 2-2.5 multiply 108 **platelets**/ml was added to a cuvette of an aggregometer. Peptides to be examined were added to the cuvette and the mixture stabilized for a few moments. Once the baseline was stabilized, **gamma** -**thrombin** was added to determine the minimal concentration of the agonist necessary to achieve full **platelet aggregation. Aggregation** was allowed to proceed for 5 minutes before stopping. When ADP-induced **platelet aggregation** studies were performed, 1-5 mu M ADP was added to the cuvette containing **platelet**-rich plasma. 70 nM **gamma** - **thrombin** induced a full **platelet aggregatory**

response. The **aggregation** response was abolished by 0.5-1 mM RPPGF. At 0.25 mM RPPGF, **gamma** -**thrombin**-induced **platelet aggregation** was completely inhibited. RGKWC, **gamma** -**thrombin**-induced **platelet aggregation** returned to levels seen without any inhibitor. The most potent to least potent inhibitors of **gamma** -**thrombin**-induced **platelet aggregation** are RGKLC, RGKTC, RGKRC, RGKIC, RGKWC, RGKYC, and RGKMC in decreasing order.

USE - The invention is useful for preventing **thrombosis**, where **thrombosis** is defined as occlusion of a vessel due to formation of a **platelet**-rich, fibrin-rich, or a mixed **platelet**-fibrin thrombus (claimed). The invention can be used for patients with acute coronary syndromes (e.g. cresendo angina, myocardial infacrtion) and for individuals who have acute coronary syndromes and receive percutaneous transluminal coronary angioplasty with an artificle stent placement.

Dwg.0/6

FS CPI

FA AB; DCN

MC CPI: B04-C01A; B04-C01B; B04-C01C; **B04-H19**; B14-F01B; B14-F04

TECH UPTX: 20010425

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The method further comprises inhibiting **thrombin** induced calcium mobilization in fibroblasts. The method preferably comprises inhibiting **thrombin activation** in a sample comprising blood **platelets**, which involves providing a solution comprising blood **platelets** and **thrombin** at a concentration effective to cause **platelet aggregation**, and contacting the blood sample with (I) or (II).The method further involves inhibiting **thrombin** induced **platelet aggregation.**

Preferred Composition: **Thrombin** comprises **alpha**-**thrombin** and/or **gamma**-**thrombin.**

(I) or (II) comprises at most 5 amino acids in sequence. The cell comprising **PAR1** is selected from **platelets**, endothelian cells, brain cells, fibroblasts or smooth muscle cells.

ABEX UPTX: 20010425

SPECIFIC SEQUENCES - S1 comprises a sequence selected from any one of the 17 sequences of 5 amino acids in length, of (I), such as Arg-Gly-Lys-Leu-Cys, or from any one of the 18 sequences of 5 amino acids in length, of (II), such as Arg-Gly-Asp-Trp-Cys (claimed).

ADMINISTRATION - The purified peptides of the invention may be used prophylactically in surgery or catheterization for insertion of artificial dacron grafts and stents to prevent reocclusion. Administration includes intravenous, intranasal, or oral or preferably parentally. Dosages range from 10 to 30 mg per day per kg of body weight. In preferred intravenous administration the dosage is 10 mg/kg body weight in 5 ml of normal saline or in a suitable vechile at 1 ml/min.

EXAMPLE - Three successive combinatorial libraries were prepared to obtain the peptide analogs. The first library started with the peptide Arg-Pro-Pro-Gly-Phe. Investigations showed that an alanine substitution in the peptide at position 1 at N-terminal end resulted in marked loss of **thrombin** inhibitory activity. Alternatively, substitution in the fifth position at C-terminal end of a cysteine for a phenylalanine did not result in any loss of activity. Since cysteine in this fifth position promoted binding of the peptides to plastic plates, all subsequent peptides had cysteine placed at this position. The initial positional peptide combinatorial library consisted of H-RO2XXC-NH2, H-RXO3XC-NH2 and H-RXXO4C-NH2, where O2, O3 or O4 represents all L-amino acids from A to Y, except cysteine, and X is an equimolar mixture of L-amino acids from A to Y, except cysteine. Investigations revealed that a glycine in the second position produced a peptide(s) with best ability to inhibit **thrombin**-induced **platelet aggregation**, to

inhibit **thrombin**-induced calcium mobilization, and to bind biotin-NAT112 (peptide sequence Asn-Ala-Thr-Leu-Asp-Pro-Arg-Ser-Phe-Leu-Leu-Arg that spans the **alpha-thrombin** cleavage site on the **thrombin receptor**). A second peptide combinatorial library was designed to examine the third and fourth position of this sequence. Peptides H-RGO3XC-NH2 and H-RGXO4C-NH2 were prepared where O3 and O4 were all L-amino acids from A to Y, except cysteine, and X was an equimolar mixture of L-amino acids from A to Y, except cysteine. Investigations revealed that a lysine or aspartic acid in the third position produced peptides with best ability to inhibit the above-mentioned processes. A third library was prepared where the third positions were fixed as a lysine or aspartic acid, H-RGKO4C-NH2 and H-RGDO4C-NH2, where O4 is all L-amino acids except cysteine. A standard solid phase automated peptide synthesis was utilized to prepare the peptide libraries. Synthetic peptide libraries were prepared using methylbenzhydrylamine (MBHA) polystyrene resin and standard t-Boc chemistry in combination with simultaneous multiple peptide synthesis (SMPS). A peptide synthesis resin was prepared that assures equimolarity of the peptides on the resin. Nineteen porous polypropylene packets, each containing 4.65 mmol of MBHA resin, were coupled to each of the protected N-**alpha**-t-Boc amino acids of interest. Cysteine was excluded from coupling mixture. The resulting resins from each packet were combined and thoroughly mixed. The resin mixture was then separated into 19 portions of equal weight which were then placed into porous polypropylene packets, followed by N-**alpha**-t-Boc protecting group removal and neutralization of the resulting amine TFA salts. Resin packets were then reacted with solutions of the individual **activated** amino acids to yield the various peptide combinations. The peptide mixtures were deprotected and then cleaved from their respective resins using low-high hydrogen fluoride. Extraction of the individual peptide mixtures was carried out with water or dilute acetic acid and the solutions lyophilized.

L84 ANSWER 11 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **1999-633640** [54] WPIX
DNC **C1999-185014**
TI Novel **protease activated receptor** 4, useful for screening for (ant)agonists for promoting the proliferation and/or differentiation of **platelets** and in mediating inflammatory events.
DC B04 D16
IN FOSTER, D C; PRESNELL, S R; XU, W; YEE, D P
PA (UNIW) UNIV WASHINGTON; (ZYMO) ZYMOGENETICS INC; (FOST-I) FOSTER D C; (PRES-I) PRESNELL S R; (XUWW-I) XU W; (YEED-I) YEE D P
CYC 82
PI WO 9950415 A2 19991007 (199954)* EN 85p C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9934591 A 19991018 (200010)
US 6111075 A 20000829 (200043) C07K007-06
US 6436400 B1 20020820 (200257) C07K016-28
US 2003143218 A1 20030731 (200354) A61K038-48
ADT WO 9950415 A2 WO 1999-US7100 19990331; AU 9934591 A AU 1999-34591 19990331; US 6111075 A US 1998-53866 19980401; US 6436400 B1 Div ex US 1998-53866 19980401, US 2000-479130 20000107; US 2003143218 A1 Cont of US 1998-53866 19980401, Div ex US 1999-371333 19990810, Div ex US 2000-479130 20000107, Div ex US 2000-480720 20000107, US 2002-187049 20020628
FDT AU 9934591 A Based on WO 9950415; US 6436400 B1 Div ex US 6111075; US 2003143218 A1 Cont of US 6111075, Div ex US 6436400

PRAI US 1998-53866 19980401; US 2000-479130 20000107
IC ICM A61K038-48; C07K007-06; C07K016-28; C12N015-12
ICS A61K038-17; C07H021-04; C07K007-08; C07K014-705; C12N005-06; C12P021-02
AB WO 9950415 A UPAB: 20010312
NOVELTY - A **protease activated receptor** 4 (**PAR4**) polypeptide (I), is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) an isolated polynucleotide (PN) (II) encoding (I), comprising nucleotides 176 to 1330 of the 4895 base pair sequence fully defined in the specification (I), or its derivatives;
(2) an isolated **PAR4** ligand (III), comprising amino acids 48 (Gly) to 53 (Val) of (I), or allelic variants or orthologs of (III);
(3) an isolated polynucleotide encoding (III), comprising nucleotides 317 to 409 of the 4895 nucleotide sequence fully defined in the specification, or its derivatives;
(4) an expression vector (IV) comprising the following operably linked elements:
(a) a transcription promoter;
(b) a DNA segment (I); and
(c) a transcription terminator;
(5) an antibody that binds to an epitope of the polypeptide (II); and
(6) a culture cell containing (IV).
USE - (I) can be used to screen for its agonists and antagonists. Agonists of (I) are useful for upregulating cellular or physiological responses whereas antagonists are used to down-regulate these activities. The **PAR4** polypeptide is further useful for dissecting the effects of **thrombin** or other **activating proteases** in the clotting **pathway** from the effects of these **proteases** at the cellular level. Agonists are specifically useful in promoting the proliferation and/or differentiation of **platelets**, in mediating inflammatory events, responses to vascular injury, chemotaxis or mitogenesis, and in producing growth factors. Antagonists are useful as research reagents for characterizing sites of ligand-**receptor** interaction.
Dwg.0/1
FS CPI
FA AB; DCN
MC CPI: B04-C01G; B04-E03D; B04-G04; B04-K01R; B04-L01; B04-L06; B04-N04A; B11-C07A; B11-C08E4; **B12-K04E**; **B12-K04F**; B14-F02; D05-H08; **D05-H09**; D05-H11; D05-H12A; D05-H12E; D05-H13; D05-H14; D05-H17A4
TECH UPTX: 19991221
TECHNOLOGY FOCUS - BIOTECHNOLOGY - The isolated **PAR4** polypeptide (I) comprises nucleotides 227 to 1330, preferably nucleotides 317 to 1330 of the 4895 base pair sequence fully defined in the specification.
ABEX UPTX: 19991221
SPECIFIC SEQUENCES - The isolated **PAR4** polypeptide (I) comprises amino acids 18 to 385 of the 385 amino acid sequence fully defined in the specification, or its derivatives.
EXAMPLE - An EST sequence was identified using a database that showed homology to the three **protease-activated receptors** in the fourth transmembrane domain. A 600 base pair DNA probe derived from this sequence was used to screen a selected lymphoma Daudi cell line cDNA library, by standard techniques. cDNA inserts were sequenced on both strands by the chain termination method, using the Sequenase Kit (US Biochemicals). A full length cDNA clone was identified, sequences on both strands and designated **protease-activated receptor** 4 (**PAR4**).

L84 ANSWER 12 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **1999-619953** [53] WPIX

DNN **N1999-457240** DNC **C1999-180904**
TI DNA molecules encoding **protease-activated receptor** 4, useful in compound assays for **thrombin** agonist and antagonist activity.
DC B04 D16 S03
IN COUGHLIN, S R; KAHN, M
PA (REGC) UNIV CALIFORNIA
CYC 24
PI WO 9943809 A2 19990902 (199953)* EN 69p C12N015-12
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP KR NO
AU 9926728 A 19990915 (200004)
NO 2000004274 A 20001013 (200063) C12N000-00
EP 1056854 A2 20001206 (200064) EN C12N015-12
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
KR 2001041418 A 20010515 (200167) C12N015-12
JP 2002504369 W 20020212 (200215) 82p C12N015-09
ADT WO 9943809 A2 WO 1999-US2983 19990211; AU 9926728 A AU 1999-26728 19990211; NO 2000004274 A WO 1999-US2983 19990211, NO 2000-4274 20000825; EP 1056854 A2 EP 1999-906934 19990211, WO 1999-US2983 19990211; KR 2001041418 A KR 2000-709552 20000828; JP 2002504369 W WO 1999-US2983 19990211, JP 2000-533549 19990211
FDT AU 9926728 A Based on WO 9943809; EP 1056854 A2 Based on WO 9943809; JP 2002504369 W Based on WO 9943809
PRAI US 1998-32397 19980227
IC ICM C12N000-00; C12N015-09; C12N015-12
ICS A61K038-00; A61K038-17; A61K038-48; A61K045-00; A61P007-02; A61P009-10; A61P017-02; A61P029-00; C07K014-705; C07K016-28; C12N001-19; C12N001-21; C12N005-10; C12N009-74; C12Q001-00; G01N033-68
AB WO 9943809 A UPAB: 19991215
NOVELTY - Nucleic acids encoding a **protease-activated receptor** 4 (**PAR4**) and the corresponding recombinant polypeptides, are new.
DETAILED DESCRIPTION - The DNA encodes an amino acid sequence of 397 (I) or 386 (II) amino acids (aa; given in the specification) and has sequence of 1360 (III) or 1534 (IV) base pairs (bp; given in the specification) or degenerate sequences of (III) and (IV).
INDEPENDENT CLAIMS are also included for the following:
(1) a purified DNA which has 50 % or greater identity to (III) or (IV) and where the DNA selectively hybridises to sequences complementary to (III) and (IV);
(2) an isolated **PAR4** polypeptide;
(3) a purified polypeptide (A) which is **activated** by **thrombin** and mediates phosphoinositide hydrolysis in a cell expressing the polypeptide on its surface;
(4) a fragment or analog of a polynucleotide encoding the purified polypeptide;
(5) a purified **PAR4 activating** peptide;
(6) an antibody which selectively binds to (A);
(7) a vector comprising the DNA of (III) or of claim (1);
(8) a cell comprising the vector of claim (7); and
(9) an assay device comprising a support surface and a cell of claim (8) or membranes derived from the cell of (8).
ACTIVITY - Cardiant; coagulant; anticoagulant; antiarteriosclerotic; anti-inflammatory; nephrotropic; hemostatic; vulnerary.
MECHANISM OF ACTION - **Thrombin-PAR4** interaction promoter and/or inhibitor.
USE - The recombinant **receptor** polypeptides, **receptor** fragments and analogs expressed on the surface of cells are useful in methods for screening candidate compounds for their ability to act as agonists or antagonists to the effects of the interaction between **thrombin** and **PAR4**. Reaction-agonists may be

used as therapeutics to treat wounds, promote clotting and as reagents to **activate platelets** in diagnostic tests.
Reaction-antagonists may be used to control blood coagulation, treat heart attacks and strokes and block inflammatory and proliferative responses to injury (as occur in normal wound healing and variety of diseases including atherosclerosis, restenosis, pulmonary inflammation (ARDS) and glomerulosclerosis). Antibodies of the invention are immunoreactive or immunospecific for and therefore specifically bind to a **PAR4** protein and may be used as screening agents or reaction antagonists.

The **PAR4 receptor** is **activated** by **thrombin** with subsequent phosphoinositide hydrolysis, Ca2+ efflux and **platelet aggregation. Activation** of leukocytes, mesenchymal cells in response to wounding also occurs as well as mediating signaling in embryonic development. The ability of **PAR4** to mediate signaling by **alpha -thrombin** was tested. Xenopus oocytes were microinjected with mouse **PAR4** cRNA. This conferred **thrombin**-dependent 45Ca mobilization which reflected agonist-triggered phosphoinositide hydrolysis.

ADVANTAGE - A novel **thrombin receptor** **PAR4** is disclosed making it possible to identify novel **thrombin** agonists and antagonists which may not be identifiable via **PAR1**, **PAR2** or **PAR3 receptors.**
This **receptor** also makes it possible to obtain additional information regarding **thrombin activation** and the sequence of biochemical events initiated.
Dwg.0/15

FS CPI EPI
FA AB; DCN
MC CPI: B04-C01G; B04-E02F; B04-E05; B04-E08; B04-F0100E; B04-F0700E; B04-G04; B04-G0400E; B11-C07A; B11-C08E5; **B12-K04E**; **B12-K04F**; B14-C03; B14-F01B; B14-F04; B14-F07; B14-F08; B14-L01; B14-L02; B14-N17B; D05-C12; **D05-H09**; D05-H11; D05-H12A; D05-H12B; D05-H12D1; D05-H12E; D05-H14; D05-H17A6; D05-H18B
EPI: S03-E14H
TECH UPTX: 19991215

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Polypeptide: The purified polypeptide of (3) has the sequence of (I) or (II).
Preparation: The DNA, **receptor** or **receptor** fragment is derived from a vertebrate animal, preferably a human or mouse. However, the gene can be chemically synthesized.

ABEX UPTX: 19991215

SPECIFIC SEQUENCES - (I) represents an amino acid sequence of a **PAR4** protein comprising a disclosed sequence of 397 amino acids. (II) represents an amino acid sequence of a **PAR4** protein comprising a disclosed sequence of 386 amino acids. (III) represents a polynucleotide sequence encoding **PAR4** comprising a disclosed sequence of 1360 bp. (IV) represent a polynucleotide sequence encoding **PAR4** comprising a disclosed sequence of 1534 bp.

EXAMPLE - The public expressed sequence tag (EST) database was searched for potential **PAR** sequences by identifying sequences with homology to **PAR1**, **PAR2** and **PAR3.** One EST clone, 400689, was identified showing similarity over an eleven amino acid stretch and was further characterized. The EST sequence was used to obtain mouse and human cDNA and genomic clones by a combination of PCR and hybridization techniques. The human **PAR4** sequence was obtained using degenerate PCR primers to amplify a 900 bp dominant product from total human genomic DNA. PCR was performed and sequencing of the 900 bp products revealed a novel amino acid sequence that was 88 % identical to mouse **PAR4.** Human megakaryocytic cell lines were screened for **PAR4** expression by Northern analysis using the 900 bp product as a probe and the K562 erytholeukemia cell line was found to be positive. 5'RACE and nested PCR reactions using two reverse primers were performed.

A dominant 350 bp band was observed, subcloned and sequenced, providing the sequence to the hPAR4 start codon. The same kit and template were used for 3'RACE. The GIBCO UAP primer was used as a reverse primer and hemi-nested PCR was then performed. A dominant 1.6 kb band was observed, subcloned and sequenced, and provided the sequence for a stop codon. A functional hPAR4 clone was created by PCR using Vent polymerase with primers from the start codon to 50 bp beyond the stop codon using 25 cycles of PCR and K562 template cDNA. The PCR product was sequenced and subcloned into an oocyte expression vector for generating cRNA (pFROGGY). Human **PAR4** cRNA was microinjected into Xenopus oocytes to study its function.

L84 ANSWER 13 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN **1998-271905** [24] WPIX
DNN **N1998-213491** DNC **C1998-084844**
TI DNA encoding **protease-activated receptor** 3 - for detection of specific agonists and antagonists, potentially useful for treating e.g. **thrombosis**, atherosclerosis, inflammation etc..
DC B04 D16 S03
IN CONNOLLY, A; COUGHLIN, S R; ISHIHARA, H
PA (REGC) UNIV CALIFORNIA
CYC 21
PI WO 9818456 A1 19980507 (199824)* EN 74p A61K031-00
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP
US 5892014 A 19990406 (199921) C12N015-12
EP 948323 A1 19991013 (199947) EN A61K031-00
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001510988 W 20010807 (200150) 74p C12N015-09
ADT WO 9818456 A1 WO 1997-US19732 19971029; US 5892014 A US 1996-742440 19961030; EP 948323 A1 EP 1997-946388 19971029, WO 1997-US19732 19971029; JP 2001510988 W WO 1997-US19732 19971029, JP 1998-520768 19971029
FDT EP 948323 A1 Based on WO 9818456; JP 2001510988 W Based on WO 9818456
PRAI US 1996-742440 19961030
IC ICM A61K031-00; C12N015-09; C12N015-12
ICS A61K035-00; A61K038-00; A61K045-00; A61P007-02; C07K014-435; C07K014-705; C12N001-15; C12N001-19; C12N001-21; C12N005-10; C12N015-63; C12P021-02; C12Q001-34; G01N033-15; G01N033-50; G01N033-53; G01N033-566
AB WO 9818456 A UPAB: 19991122
DNA (I) encoding a **protease-activated receptor** 3 (**PAR3**) is new.

Also claimed are:

(1) an isolated **PAR3** protein (II), and its fragments or homologues that include a domain **activatable** by **thrombin** and mediate hydrolysis of phospho-inositide (PI);

(2) a vector containing (I);

(3) a cell containing (2);

(4) an assay device containing these cells on a support surface;

(5) a composition containing an (ant)agonist of **PAR3** ligand (PAR3L; especially **thrombin**) plus a carrier.

USE - Cells of (3) are used to screen for (ant)agonists of PAR3L.

(II) and agonists are useful in treatment of **thrombosis**, atherosclerosis, re-stenosis and other **thrombin**-related diseases.

Antagonists are potentially useful for mediating inflammatory and proliferative responses to injury (as in normal wound healing), also atherosclerosis, re-stenosis, pulmonary inflammation and glomerulo-sclerosis, and formation of clots that cause stroke and heart attacks.

Agonists and antagonists are preferably administered intravenously, but may also be given orally, nasally or topically.

ADVANTAGE - Cells of (3) allow identification of (ant)agonists that

can not be identified by **PAR1** or 2.
Dwg.6/10
FS CPI EPI
FA AB; GI
MC CPI: B04-E01; B04-E08; B04-F01; B04-K01; **B12-K04**; B14-C03;
B14-F04; B14-F07; B14-N10; **D05-H09**; D05-H10; D05-H12A;
D05-H12E; D05-H14
EPI: S03-E14H4

=> d his

(FILE 'HOME' ENTERED AT 06:14:06 ON 09 MAR 2004)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 06:14:23 ON 09 MAR 2004
L1 1 S US20020103107/PN
E SOSLAU G/AU
L2 42 S E3-E5
E (GP OR GLYCOPROTEIN OR GLYCO PROTEIN)()(IB OR 1B OR (I OR 1)(
L3 2133 S (GP OR GLYCOPROTEIN OR GLYCO PROTEIN)()(IB OR 1B OR (I OR 1)(
E GLYCOPROTEIN/CT
E E57+ALL
L4 364 S E2
L5 724 S GLYCOPROTEIN#/CW (L) (1B OR IB OR GP1B OR GPIB)
E PAR/CT
E E6+ALL
L6 280 S E2
L7 308 S E5
L8 50 S E7
L9 92 S E9
L10 13417 S (PAR OR ((PROTEINASE OR PROTEASE)()ACTIVAT?()RECEPTOR)(5A)(1
L11 13414 S (PAR OR ((PROTEINASE OR PROTEASE)()ACTIVAT?()RECEPTOR)()(1 OR
L12 10684 S L10,L11 NOT RECEPTOR
L13 2733 S L10,L11 NOT L12
L14 4881 S L3-L9,L13
E DRUG SCREENING/CT
L15 22652 S E3-E5
E E3+ALL
L16 28787 S E2,E1+NT
E E5+ALL
L17 7824 S E3
E E14+ALL
L18 3025 S E1
E E2+ALL
E DRUG/CT
E E10+ALL
L19 15561 S E3
E DRUG/CT
L20 882 S E13
L21 8110 S E230+NT OR E231
L22 4500 S E262 OR E263
E DRUG SCREENING+ALL/CT
E E7+ALL
L23 156 S E2
L24 78 S L14 AND L15-L23
L25 137 S L14 AND SCREEN?
L26 163 S L24,L25

FILE 'REGISTRY' ENTERED AT 06:26:53 ON 09 MAR 2004
L27 1 S THROMBIN/CN

FILE 'HCAPLUS' ENTERED AT 06:27:59 ON 09 MAR 2004

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L28       16686 S L27
L29       31055 S THROMBIN
L30         118 S BLOOD()(COAGULAT? OR CLOT?)()FACTOR()(IIA OR II()ACTIVAT?)
L31         463 S THROMBASE OR THROMBINAR OR THROMBOFORT OR THROMBOSTAT OR TROP
L32       31683 S L28-L31
L33          48 S L26 AND L32
L34          33 S L26 AND PLATELET(L)AGGREGAT?
                E CELL AGGREGATION/CT
L35           7 S E3,E4 AND L26
                E E3+ALL
L36          15 S E1+NT AND L26
                E PLATELET/CT
L37          30 S L26 AND E3-E27
                E E28+ALL
L38           7 S L26 AND E3
                E PLATELET/CT
                E E33+ALL
L39          16 S L26 AND E6,E5
                E E4+ALL
L40          27 S L26 AND E5,E4+NT
L41          40 S L26 AND (E12+NT OR E13+NT OR E14+NT)
L42          11 S L26 AND (E16+NT OR E17+NT)
L43          20 S L26 AND (ANTITHROMBO? OR ANTIPLATELET? OR ANTI()(THROMBO? OR
L44          92 S L33-L43
L45           1 S L2 AND L26
L46           1 S L2 AND L44
L47           1 S L1,L45,L46
L48          41 S L2 NOT L47
                SEL DN AN 1 3 10 18
L49           4 S E1-E12 AND L48
L50           5 S L47,L49
L51          91 S L44 NOT L50
L52          32 S L41 AND (PY<=2000 OR PRY<=2000 OR AY<=2000)
                SEL DN AN L52 4 7 19 26 28
L53           5 S E13-E27
L54          10 S L50,L53
L55          59 S L51 NOT L52-L54
                SEL DN AN L55 7 14-18 23 27 29 30 32 33 35 40-43
L56          17 S E28-E70
L57          27 S L54,L56 AND L1-L26,L28-L56
L58          27 S L57 AND (PAR# OR PAR()(1 OR 2 OR 3 OR 4) OR PLATLET?(L)ACTIVA
L59          27 S L58,L***

     FILE 'REGISTRY' ENTERED AT 07:06:59 ON 09 MAR 2004

     FILE 'HCAPLUS' ENTERED AT 07:07:09 ON 09 MAR 2004

     FILE 'BIOSIS' ENTERED AT 07:07:53 ON 09 MAR 2004
                E SOSLAU G/AU
L60          67 S E3,E4
L61          30 S L60 AND (00520/CC OR (CONGRESS? OR CONFERENCE? OR POSTER? OR
L62           4 S L61 AND ARTICLE/DT
L63          26 S L61 NOT L62
                SEL DN AN L63 1-3 5 7 8 11
L64           7 S L63 AND E1-E14

     FILE 'BIOSIS' ENTERED AT 07:12:26 ON 09 MAR 2004

     FILE 'WPIX' ENTERED AT 07:12:50 ON 09 MAR 2004
L65         595 S C12Q001-56/IC,ICM,ICS
L66        1482 S L3/BIX
L67          45 S ((PROTEINASE OR PROTEASE)()ACTIVAT? RECEPTOR?)/BIX
L68         161 S (PAR1 OR PAR2 OR PAR3 OR PAR4 OR PAR()(1 OR 2 OR 3 OR 4))/BIX
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L69          365 S ((ALPHA OR ALFA OR BETA OR GAMMA)(S)THROMBIN)/BIX
L70           22 S L65 AND L66-L69
L71            0 S L65 AND L67
L72            1 S L65 AND L68
L73            5 S ((ALPHA OR ALFA OR BETA OR GAMMA)()THROMBIN)/BIX AND L65
L74            7 S L67,L68 AND (B04-H19 OR C04-H19 OR B04-B04D3 OR C04-B04D3)/MC
                 SEL DN AN 1 3-5
L75            4 S E15-E23
L76            4 S L72,L75
                 E SOSLAU G/AU
L77            2 S E3
L78            5 S L76,L77
L79            5 S L78 AND (PAR# OR PLATELET? OR ACTIVAT? OR RECEPTOR OR GP? OR
L80           33 S L67,L68 AND (B12-K04# OR C12-K04# OR D05-H09)/MC
L81           30 S L80 NOT L70-L79
                 SEL DN AN 1 4 9 12 14 25 26 28
L82            8 S E1-E21
L83            8 S L82 AND (PAR# OR PLATELET? OR ACTIVAT? OR RECEPTOR OR GP? OR
L84           13 S L79,L83 AND L65-L83

     FILE 'WPIX' ENTERED AT 07:41:09 ON 09 MAR 2004

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